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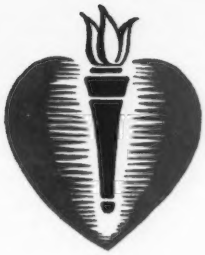

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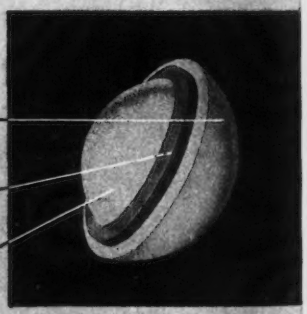

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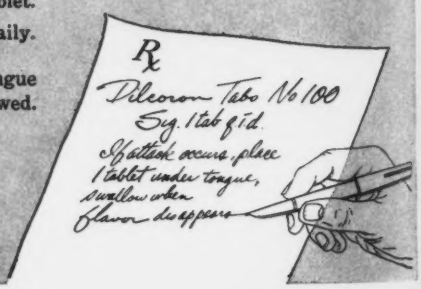

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Editorial

In the Best Interest of the Patient

MODERN cardiac surgery has brought into sharp focus the benefits to be gained by the patient from effective teamwork by a multidisciplined medical team. Usually included on such a team are physicians skilled in cardiology, radiology, cardiopulmonary hemodynamics, anesthesiology, and surgery. The patient's welfare is best served by careful consideration of his total problem by the group, individually and in conference. Teaching is also most effective under these circumstances at all levels of medical education, undergraduate, graduate, and postgraduate.

It is therefore surprising that in care and teaching dealing with other areas of the vascular system such teamwork has not been so generally adopted. Less than 15 years ago there was a clear-cut division into 2 camps, usually composed of internists versus surgeons. They held sharply to differences in a large number of questions such as the efficacy and scope of sympathectomy for peripheral arterial insufficiency, the use of surgical interruption of veins, and the value of anticoagulants in the control of thromboembolic disease. More recently sharp differences of opinion have been expressed regarding the value of direct surgical procedures for the relief of femoral arterial occlusions and in the management of peripheral arterial emboli.

Both internists and surgeons have made good cases for their positions and most patients are treated effectively. However, is it not almost always in the patient's best interest for a surgically minded internist and a medically minded surgeon to confer closely on his vascular problem? If this is self-evident, then how is it to be accomplished? The ideal meeting ground for joint observation of patients is in a combined clinic where internists and surgeons study and treat patients with a free and critical exchange of ideas. From the clinic the in-hospital patients should have the identical supervision. Students learn that mature judgment is gained by the distillation of the best ideas in regard to medical and surgical diagnostic and therapeutic modalities.

To cite an example: C.W., a man of 50 years, was admitted to the hospital on June 8, 1949, because of severe pain in the right thigh and calf associated with coldness and numbness of the extremity of 24 hours' duration. He was somewhat overweight, a tense and dynamic man who was a heavy smoker. Examination of the arterial system reveaied it to be grossly normal with the exception of the right lower extremity where no pulses could be palpated. The leg below the knee was cool and hypesthetic and the foot exhibited a pallid cyanosis. Oscillometric readings were 2.5 units above and 3.5 units below the knee on the left side, whereas on the right side there was no oscillation. The heart was in regular sinus rhythm, had normal sounds and the electrocardiogram was interpreted as being normal. The most likely diagnosis seemed to be an atherosclerotic thrombotic

occlusion of the right iliac artery, probably the external branch. Suggestions for therapy included sympathectomy and thrombectomy among others, but it was the writer's belief that a conservative regimen would probably save the limb and lead to some measure of function. Such a program and the possible results to be had from it had been learned at the knee of one of the senior members of this Journal's Editorial Board who is an internist. The program included elevation of the head of the bed on 6-inch blocks, reflex heat to the abdomen, protective cotton padding to the extremity protected by an unlit cradle, and abstinence from tobacco. Not only did the extremity survive, but 9 years later the patient has no limitation in walking and readily palpable pedal pulses in the affected foot.

With the developments of the past 10 yea it is quite likely that a patient presenting similar problem would today have an ele tively timed operative procedure such thromboendarterectomy or a bypass with plastic prosthesis. Whether the long-term r sult would be as good, cannot be answered this time.

It seems clear that the integrated clin staffed by internists and surgeons interest in cardiovascular problems with coordinat in-hospital supervision will function in t patients' best interest. In actual practice t constant rubbing of minds generates spar that are often revealing and even surpri their originators. In the experience of th author this brings to the staff the deepe of satisfactions.

JERE W. LORD, JR.

A word or two upon an ethical problem which is often very perplexing—viz., What is your duty in the matter of telling a patient that he is probably the subject of an incurable disease? I can give you no hard-and-fast rule; the temperament of the individual himself, his associations and responsibilities, your own convictions as to the seriousness of the condition—all these must be carefully weighed. The question is somewhat theoretical, since in reality the necessity does not often arise. The announcement has already been made, for no man suffers the anguish of a severe paroxysm of angina without a consciousness of the nearness of the Angel of Death. We are sometimes, I confess, placed in positions of the utmost delicacy, since a man may have not the slightest intimation of his parlous state, and you may become aware of the urgent necessity that he should make proper arrangements to protect his wife and children. In such a case a quiet hint as to the uncertainty of the outlook in heart and artery disease may be enough to set him a-thinking; or, in the case of an "evenbalanced soul," the whole question may be discussed frankly. One thing is certain: it is not for you to don the black cap, and, assuming the judicial function, take hope from any patient—"hope that comes to all"—and you may dwell with advantage on the aspects of John Hunter's case rather than on those of Thomas Arnold.—WILLIAM OSLER. *Lectures on Angina Pectoris and Allied States*, 1897.

Disseminated Nodular Pulmonary Ossification in Patients with Mitral Stenosis

By WILLIAM R. WILSON, M.D., RIKURO SASAKI, M.D., AND CHARLES A. JOHNSON, M.D.

What seem to be rare complications of common diseases may merely be uncommon because no one accumulates a large number. The unusual combination of disseminated nodular bone formation in the lungs and chronic mitral stenosis is more common in young men. The clinical findings in 4 cases are described and the pathogenesis is discussed.

IN RECENT YEARS clinicians have had to think of histoplasmosis as well as tuberculosis when confronted with diffuse nodular calcific shadows in the lung parenchyma. Disseminated bone formation in the lung is rare, though a form associated with mitral stenosis has been recognized for many years. It is our purpose to review our experience with 4 cases of disseminated bone formation in mitral stenosis, to review autopsy-proved case reports, and to discuss the controversial question of pathogenesis.

The combination of pulmonary ossification and mitral stenosis occurs primarily in young men from 21 to 40 years of age. The predominance of men is remarkable considering the more frequent occurrence of mitral stenosis in women. Presenting symptoms and major physical signs are merely those accompanying ordinary mitral stenosis. Invariably congestive failure has occurred during the course of the disease. Hemoptysis is an infrequent presenting symptom, although a few patients Radiologic examination shows the characteristic findings of mitral stenosis and many have had severe pulmonary hemorrhage. dense opacities throughout the lung fields. The apices are usually clear and the opacities are more numerous in the right lung field, especially in the lower lobe. Similar x-ray findings can be seen in severe pulmonary hemosiderosis.[1-4] The radiologic differentiation is often quite difficult. Other opacities that must be considered include those of miliary tuberculosis, histoplasmosis, pneumoconiosis, arteritis, sarcoidosis, metastatic carcinoma, aspergillosis, bilharziasis, bronchopneumonia, bronchitis obliterans, chronic passive congestion, polycythemia, brucellosis, tularemia, psittacosis, leukemia, Hodgkin's disease, lupus erythematosus, and xanthomatosis.

The results of cardiac catheterization have been reported in a few patients. Moderate to severe pulmonary hypertension and increased pulmonary vascular resistance were found.[5]

Gross pathologic characteristics are the numerous granular, yellow to white, discrete nodules of bony consistency, usually measuring 2 to 8 mm. in diameter. The nodules are scattered throughout both lung fields, but often are concentrated near the pleura in the lower lobes. These nodules are distinctly different from diffuse forms of bone formation in the lung, such as the variety occasionally seen in old men, which is thought to come from metaplasia resulting from senile alterations in the perivascular connective tissue.[6] Branching or racemose spicules of bone run into the septum of the lung, often for some

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This study was supported in part by grants from the Iowa Heart Association and the Iowa Tuberculosis and Health Association.

TABLE 1.—*Clinical Data of Documented Cases*

Author	Year	Sex	Age	History of rheumatic fever	Other valvular lesions	Method of verification
Wagner[11]	1859	M	26	No	Tricuspid stenosis Aortic insufficiency	Autopsy
Derischanoff[12]	1930	M	21	No	Mitral insufficiency	Autopsy
Salinger[13]	1932	M	31	No	None	Autopsy
Wells and Dunlap[14]	1943	F	34	No	None	Autopsy
Grishman and Kane[15]	1945	M	29	Yes	Mitral insufficiency	Autopsy
Elkeles and Glynn[7]	1946	M	32	No	Aortic insufficiency	Autopsy
Elkeles[16]	1947	M	32	No	None	Autopsy
Lawson[17]	1949	F	39	Yes	Aortic stenosis	Autopsy
Steiner and Goodwin[18]	1954	M	32	No	?	Biopsy
Haubrich[19]	1954	F	24	Yes	None	Biopsy
		M	23	No	Mitral insufficiency	Autopsy
		M	22	No	Mitral insufficiency	Biopsy
		M	27	No	Atrial septal defect	Autopsy
Whitaker, Black, and Warrack[20]	1955	M	30	Yes	Mitral insufficiency	Autopsy
		M	27	No	None	Biopsy
		M	38	No	None	Autopsy
		M	38	No	Mitral insufficiency	Biopsy
Daugavietis and Mautner[21]	1957	M	30	Yes	Mitral insufficiency	Autopsy
Fleming and Robinson[5]	1957	M	24	Yes	?	Biopsy
		M	30	No	?	Biopsy
		M	40	Yes	?	Biopsy
		M	34	No	?	Biopsy
		M	35	No	?	Biopsy

distance. This process usually is more localized than the nodular type associated with mitral stenosis. In addition to nodular ossification, various pulmonary complications of mitral valve disease, such as congestion, induration, hemorrhage, or infarction, often occur.

The bony nodules vary in size. Usually they are round or mulberry-shaped. Characteristically they begin within alveoli or alveolar sacs. The larger nodules, often 6 to 8 mm. in diameter, overlap several adjacent air spaces. Osteocytes and small vascular channels can often be seen. Osteoid tissue and some osteoblasts usually are found in the periphery of the bony nodules. Elkeles and Glynn[7] found that the framework of the lung was incorporated in the developing bone. Stains for elastic tissue demonstrated the continuity of the elastic tissue of the lung with that in the bone. The nodules are not adherent to the alveolar walls in the majority of cases. The pathologist often has difficulty in obtaining satisfactory sections showing the ossification because the nodules of bone are shelled out so easily.

Microscopic examination of the lungs usually reveals marked congestion, patchy increase in interstitial connective tissue, particularly in the perivascular areas, and numerous hemosiderin-containing macrophages in the alveoli, bronchial lumina, and interstitial spaces. In some areas the macrophages are arranged in small clusters. An exudate of homogeneous fibrinoid material in various stages of organization may be seen in the alveoli. No evidence of calcification can be found in the lungs in contrast to pulmonary alveolar microlithiasis, in which calcification is the main finding, and bone formation is rare.[8–10]

We were able to find only 23 cases adequately documented by autopsy or lung biopsy (table 1). Other cases have been reported on the basis of radiologic examination, but lacked pathologic confirmation.[1,15,22–26] Only 3 confirmed cases were found in the American literature.[14,15,21]

The hospital records of 533 patients with mitral stenosis, with or without mitral insufficiency or aortic valve disease, seen from 1952 to 1958, were reviewed. In addition, autopsy protocols of the 175 cases of mitral stenosis from 1935 to 1952 were surveyed. Three instances of nodular bone formation in the lungs were discovered. The fourth example is of a man who recently had a mitral commissurotomy and lung biopsy.

Case Reports

Case 1. D. H., a 30-year-old taxi driver, was first seen in University Hospitals in January 1943 at the age of 28. The cardiac diagnosis was rheumatic mitral stenosis with congestive heart failure. An x-ray of the chest revealed multiple "calcific densities" measuring up to 1 cm. in diameter, cardiac enlargement, and a contour consistent with mitral stenosis (fig. 1). Initially, these densities were thought to represent old healed disseminated tuberculosis. Digitalis and diuretics produced temporary improvement, but death, due to severe congestive heart failure and acute bronchopneumonia, occurred in January 1945.

At autopsy the heart weighed 600 Gm. The mitral orifice was described as that of a "button hole." No pulmonary infarcts were found. Careful palpation of the lungs revealed about 20 spherical nodules of ossification. They had no capsules. These were found throughout all lobes of both lungs and were both deep and superficial. When a nodule was shelled out, close inspection showed that the surface was finely nodular, resembling the surface of a cauliflower.

Microscopically, there were severe acute bronchopneumonia and chronic passive congestion of the lungs. The alveolar walls were thickened by collagen and fibroblasts. Clusters of hemosiderin-laden macrophages were scattered in the alveolar spaces and walls. There was much proliferation of alveolar epithelium. Some of the alveolar walls had clublike thickening.

The nodules were composed of irregular cortical-like bone with cement lines, lacunae, and osteocytes. The bone was mature (fig. 2). Haversian canals were present. The cement lines were arranged in an irregular wavy concentric pattern. Small irregular spaces in the bone contained fibrocytic connective tissue with osteoblasts and blood capillaries. No hematopoietic tissue was present. These nodules of heterotopic bone compressed and flattened the directly adjacent alveolar spaces, occupying an area equivalent to several alveolar spaces.

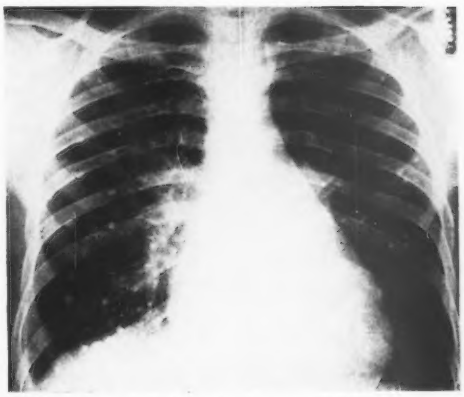

Fig. 1. Case 1. Note the characteristic mitral configuration and the multiple nodular densities.

Case 2. I. S., a 29-year-old clerical worker, was first seen in the University Hospitals in November 1941 at the age of 22. The cardiac diagnosis was rheumatic mitral stenosis. An x-ray of the chest showed occasional nodular densities in the lungs and left atrial enlargement. Calcification was seen in the mitral valve at fluoroscopy. He died 7 years later after continued episodes of congestive heart failure and a final bout of acute bronchopneumonia.

At autopsy the heart weighed 650 Gm. The mitral valve was sclerotic and stenotic, measuring 1.2 cm. by 5 mm.

Microscopic examination of the lung demonstrated severe confluent acute bronchopneumonia and chronic passive congestion. Some sections showed thickening of the alveolar walls by collagen and fibroblasts with epithelial proliferation. Emphysematous changes were seen in other areas. Clusters of hemosiderin-laden macrophages occurred in groups of adjacent alveolar spaces and just beneath the pleura. Mature, but irregularly patterned, cortical-like bone with cement lines, lacunae, and osteocytes was demonstrated in the lung parenchyma. No bone marrow was seen.

Case 3. B. M., a 36-year-old housewife, was first examined in January 1954. The cardiac diagnosis was rheumatic mitral stenosis. Congestive heart failure had been present for at least 2 years. A chronic cough productive of one-fourth cup of greenish mucopurulent sputum daily had been noted since childhood. This followed recurrent episodes of pneumonia. Cardiac fluoroscopy revealed 1+ right and left ventricular enlargement with a prominent pulmonary artery segment and 1+ left atrial enlargement. Bronchovascular markings were increased bilaterally. No nodular densities were seen in the lung fields. Cardiac catheterization was done on February 5, 1954 (table 2). On February

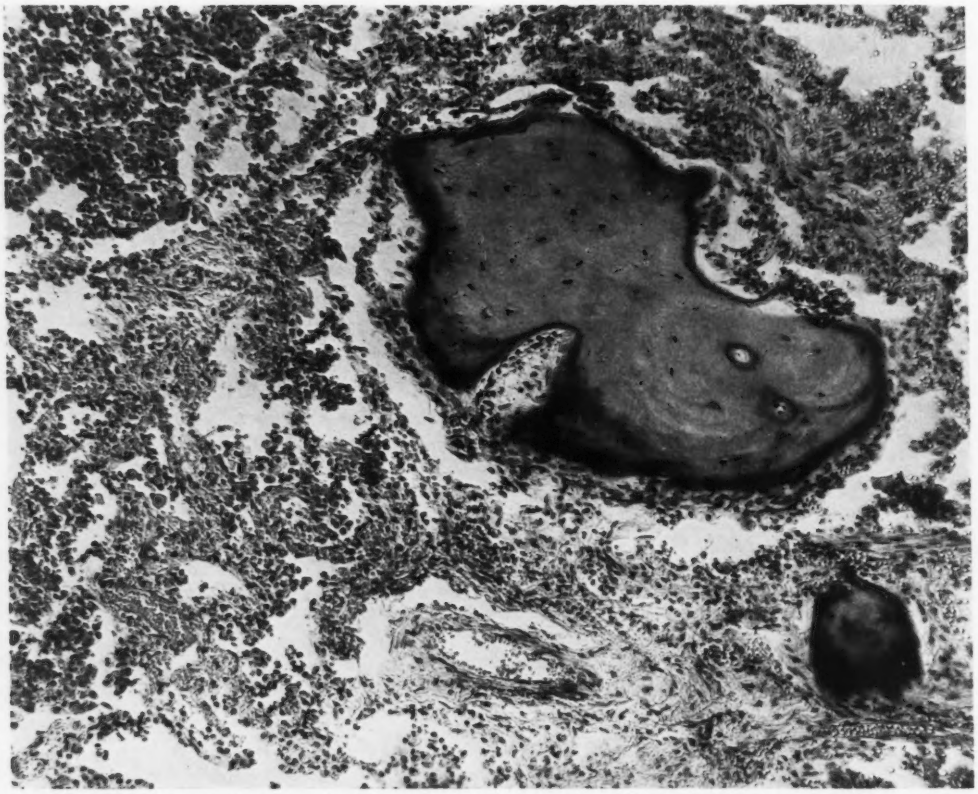

FIG. 2. Case 1. Nodules of cortical-like bone are surrounded by areas of acute bronchopneumonia superimposed upon a background of chronic congestion of the lung parenchyma. Hematoxylin-eosin stain.

9, 1954, the patient had a left thoracotomy and mitral commissurotomy. The left lower lobe and lingula showed far advanced bronchiectasis. The left upper lobe was very emphysematous. The surgeon estimated the mitral valve to be 3 mm. in diameter. The commissures were calcified. After valve fracture, the estimated opening was about 2.5 cm. in diameter. Postoperatively, her general condition deteriorated with increasing respiratory insufficiency. She died 12 days after operation.

The heart weighed 400 Gm. and was covered with a thick shaggy "bread and butter" fibrinous pericarditis. The mitral valve was still stenotic and the chordae tendineae were very thick, short, and stubby. The appearance of the right middle lobe suggested pulmonary infarction but no thrombus could be found. Microscopically, the lung tissue revealed acute necrotizing bronchopneumonia and edema. A small piece of mature heterotopic bone was found occupying an area equivalent to 5 or 6 alveolar spaces. There was mild thickening of the alveolar wall. A few areas of alveolar epithelial proliferation were found. No marrow tissue was seen.

Case 4. E. R., a 27-year-old hair dresser, was admitted to the University Hospitals on January 8, 1958. A diagnosis of rheumatic heart disease with mitral stenosis, possible mitral insufficiency, and congestive heart failure was made. A chest film revealed several circular "calcific lesions" scattered throughout the middle and lower portions of the right lung field. Bilateral bronchograms were normal. Cardiac catheterization showed no evidence of an intracardiac shunt. Moderately severe pulmonary hypertension was found (table 2). Pulmonary function studies were normal (tables and 3). A mitral commissurotomy and a lung biopsy were done on January 29, 1958. The mitral valve was calcified anteriorly. Moderate mitral regurgitation was present. The posterior commissure was opened and the valve orifice was increased in diameter from 1 cm. to 2 cm. Eight weeks post

TABLE 2.—*Cardiac Catheterization and Arterial Blood Studies*

Case no.	Pressure (mm. Hg)							Oxygen saturation (%)	P_{CO_2} (mm. Hg)
	Right pulmonary artery "wedge"	Mean	Right pulmonary artery proximal	Mean	Right ventricle	Right atrium	Mean	Femoral artery (air)	Femoral artery (air)
3 Preop.			68/33	40	65/0/5	5/1	3	86	
4 Preop.	25/16	20	59/37	41	56/0/6	8/2	4	95	47
4 Postop.		25	66/37	44	66/3/7	12/3	6	93.2	42

)peratively, cardiac catheterization and pulmonary function studies were essentially unchanged (tables 2 and 3). In April 1958 he suddenly developed acute pulmonary edema and died. An autopsy was not made.

The specimen of lung biopsy consisted of 12 Gm. of lung tissue measuring 4.5 by 2.5 by 2.5 cm. It had a rubbery consistency and cut with moderate resistance. The pleura was slightly thickened but smooth and shiny. The specimen contained several white, stony hard, irregular but generally spherical nodules measuring 3 to 4 mm. in diameter. They were easily shelled out from the lung parenchyma. They appeared to be small fragments of bone.

Microscopically the lung parenchyma was mostly collapsed. There was severe chronic passive congestion of the lungs with thickening of the alveolar walls by collagen and fibroblasts. Numerous macrophages with hemosiderin granules were seen in the collapsed alveolar spaces. There was proliferation of alveolar epithelium. The arteriolar walls were thickened by intimal proliferation. Scattered throughout the alveolar walls were small ball-like masses of hyalinized fibrous tissue. The pattern of these masses with the fibrosis was consistent with old healed rheumatic pneumonitis. The pleura was thickened by collagenous tissue. The nodules were acellular but mature bone with poorly oriented cement lines, osteoblasts, and lacunae. The cement lines described an irregular concentric oval pattern. There were irregularly shaped small spaces that contained loose fibrocytic connective tissue with hemosiderin containing macrophages, osteoblasts, and small, thin-walled capillaries. There was no hematopoietic tissue.

DISCUSSION

In 1859 Wagner[11] described bone formation in the lungs of a 26-year-old man with mitral stenosis, tricuspid stenosis, and aortic insufficiency. Similar findings were reported by Derischanoff,[12] but Salinger[13] was the first to stress the correlation between pulmonary ossification and mitral stenosis.

The incidence of discrete ossification in the lungs in chronic mitral stenosis is unknown. No statistical survey of this entity is mentioned in the previous reports. Our study of patients with mitral stenosis indicates that it is rare, since it appeared in only 4 of 708 cases.

The etiology of bone formation in the lung is not clear. Several theories have been proposed. Salinger[13] thought bone formation resulted from long-standing pulmonary congestion. Gross[24] also believed that pulmonary venous congestion was the most important factor causing transudation of plasma and red cells into the alveolar space and organization by connective tissue. Calcification then was facilitated by hemosiderin and subsequently transferred to bone. This concept was not accepted generally. Fleming and Robinson[5] found no evidence of pulmonary venous congestion in their 8 patients. No cases of bone formation have been reported in simple pulmonary congestion, although a few workers showed that venous stasis or general circulatory impairment favored bone formation in rabbit kidneys.[27,28] Daugavietis and Mautner[21] reported 1 patient with disseminated nodular pulmonary ossification and mitral stenosis, and hinted that chronic passive congestion of the lungs and damage to the liver by quinidine constituted the most likely cause. No other authors have described this combination.

TABLE 3.—*Pulmonary Function Studies, Case 4*

	Preoperative tests		Postoperative tests	
Lung volumes	Ml.	%*	Ml.	%*
Inspiratory capacity	3240	96	2720	77
Expiratory reserve volume	2170	193	1790	152
Vital capacity	5600	124	4510	96
Residual volume	1530	136	1910	162
Total lung capacity	7130	127	6420	109
Ventilation	Liters		Liters	
Minute volume				
Total	9.6		10.3	
Alveolar	4.7		5.2	
	Ml.		Ml.	
Physiologic dead space	258		255	
Alveolar gas distribution	$\%N_2$		$\%N_2$	
7-minute washout†	1.0		0.6	
Single-breath N_2 test‡	2.0		2.0	
Mechanical tests	Liters/min.	%*	Liters/min.	%*
Maximal breathing capacity	163	125	160	117
Maximal expiratory flow rate	522		429	
Maximal inspiratory flow rate	316		261	
Diffusing capacity of the lungs		Ml. CO/mm. Hg/min.		
	21		22	

*% equals per cent of predicted value based on body surface area and age.
†Normal values for 7-minute nitrogen washout are less than 2.5 per cent N_2.
‡Normal values for single-breath nitrogen test are less than 1.5 per cent N_2.

Wells and Dunlap[14] considered that nodular bone formation was the result of connective tissue proliferation, both interstitially and within the alveoli. They believed that interstitial pneumonia, usually combined with chronic passive congestion, might well be the forerunner. Congestion facilitated transformation of the connective tissue into bone. Elkeles and Glynn[7] proposed a similar hypothesis. They thought that the histologic appearance was similar to that seen in rheumatic pneumonia and that the bone nodules arose as a late complication. One of our cases (no. 4) had similar histologic findings. A majority of the reported cases, however, had not had rheumatic pneumonia. Furthermore, the entity of rheumatic pneumonia is not universally accepted.[17] Neither of these hypotheses has received much support.

Englestad[29] produced roentgen-ray pneumonitis experimentally in rabbits and noted subsequent pulmonary ossification similar to that observed in mitral stenosis.

Haubrich[19] thought hemosiderin deposition in the lungs promoted pulmonary ossification. Lawson[17] and Ellman and Gee[2] suggested that bony nodules were the end result of organization of hemosiderin deposits in the lung. They also believed that chronic passive congestion associated with pulmonary hypertension, small repeated hemorrhages, and hemosiderin deposits in clumps or macrophages were the important antecedent pathologic conditions. This explanation is not plausible, however, since bony nodules in most reported cases have only a small amount of iron.[21]

Most patients with mitral stenosis and pulmonary ossification have at least histologic evidence of hemosiderosis. Focal accumulation of hemosiderin in phagocytes forms distinct nodules in the lungs. These nodules when sufficiently large (1 to 3 mm.) become opaque, and may appear as miliary densities in the chest x-ray. Lendrum, Scott, and Park[1] believed that both hemosiderosis and

bone formation are the direct result of pulmonary hypertension and that hemosiderosis is produced by recurrent small pulmonary hemorrhages. The ossification then occurred in the fibrinous exudate of pulmonary edema, rather than as a direct result of hemosiderosis. Other authors[5,20] supported the concept of a fibrinous alveolar exudate as the site of bone formation, although they agreed that there is uncertainty about factors responsible for the exudate and its subsequent ossification.

Another hypothesis is that thrombosed septal capillaries may protrude into the alveoli, or become completely detached from the alveolar walls. Mesenchymal cells, which attach to the capillary surface, may be associated with the formation of bone.[30]

All these ideas are based on histologic and morphologic appearances. Experimental studies on heteroplastic bone formation show bone that is produced through activity of young fibroblasts.[31,32] Local calcium injection appears to stimulate ossification. Bone may be formed in old calcified lesions. Most cases with pulmonary ossification examined at autopsy had only bone formation but no unossified foci of calcification. Calcification does not seem to be a necessary precursor for bone formation. Even if it may be, transitional stages must be short and occur early in the disease.

It is unlikely that any of these factors alone is responsible. Combinations of 2 or more probably are necessary for the production of bone. Pulmonary edema, chronic passive congestion, and interstitial pneumonitis may be associated with other types of valvular disease. However, disseminated nodular pulmonary ossification has not been described in the absence of mitral stenosis.

Alteration in lung function of patients with mitral stenosis has received considerable attention in the literature.[33-36] In 1 of our patients pulmonary function tests were all normal (tables 2 and 3). No other report of pulmonary function in patients with nodular pulmonary ossification and mitral stenosis could be found. Badger, Gottlieb, and Gaensler[10] found normal pulmonary function tests in a patient with alveolar microlithiasis.

The diagnosis of bone formation in the lung should not be too difficult when mitral stenosis is evident. Skin tests with proper agents, various blood chemistries, bacteriologic studies, and, in some instances, lung biopsy may be necessary to make the correct diagnosis.

Summary and Conclusions

We have described 4 new cases of disseminated nodular pulmonary ossification associated with mitral stenosis. This rare condition occurs predominantly in young men with mitral stenosis, pulmonary hypertension, and congestive heart failure. Radiologic examination shows multiple nodular densities throughout the lung fields. The pathologic findings consist of numerous discrete nodules of bone, measuring 2 to 8 mm. in diameter, and usually located within alveolar sacs or groups of adjacent air spaces.

Detailed lung function studies in 1 patient with this rare complication of mitral stenosis were normal. Cardiac catheterization findings in this patient and in 1 other patient with the same disorder showed severe pulmonary hypertension.

The pathogenesis of disseminated nodular pulmonary ossification is still unsettled, but we agree with the suggestions of others that pulmonary hypertension, interstitial pneumonitis, and congestive heart failure may be the necessary prerequisites for the combination of disseminated nodular pulmonary ossification and mitral stenosis.

Acknowledgment

The authors are deeply grateful to Dr. William B. Bean for his encouragement and editorial assistance, and to Dr. John R. Carter for review of the microscopic findings.

Summario in Interlingua

Nos ha describite 4 nove casos de disseminate ossification nodular pulmonar, associate con stenosis mitral. Iste condition es rar e occurre predominantemente in juvene masculos con stenosis mitral, hypertension pulmonar, e congestive insufficientia cardiac. Le

examine radiologic monstra multiple densitates nodular in omne partes del campo pulmonar. Le constatationes pathologic consists de numerose nodulos discrete de osso, de diametros de inter 2 e 8 mm, usualmente locate intra saccos alveolar o in gruppos de adjacente spatios de aere.

In 1 patiente con iste rar complication de stenosis mitral, studios detaliate del function pulmonar revelava nulle anormalitate. Catheterismo cardias, in iste patiente e etiam in un altere con le mesme disordina, revelava sever hypertension pulmonar.

Le pathogenese de disseminate ossification nodular pulmonar remane indecise, sed nos nos trova de accordo con le suggestion presentate per altere autores que hypertension pulmonar, pneumonitis interstitial, e congestive insufficientia cardia es possibilemente requirimentos indispensabile in effectuar le combination de disseminate ossification nodular pulmonar con stenosis mitral.

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Medical Eponyms

By Robert W. Buck, M.D.

Basedow's Disease. The description of exophthalmic goiter which is considered classic by the Germans is that of K. Ad. von Basedow (1799-1854), a practicing physician in Merseburg. It appeared in Casper's *Wochenschrift für die gesamte Heilkunde* for March 28 and April 4, 1840, pp. 197-204 and 220-228. The article is entitled "Exophthalmos as a Result of Hypertrophy of the Cellular Tissue of the Orbit" (*Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle*).

"I have frequently observed exophthalmos caused by . . . a diseased condition of the cellular tissue of the orbit—a peculiar hypertrophy which seemed to arise as the result of disease of the heart and the larger blood vessels of certain glandular and other tissues.

"Fourteen years ago I first made the acquaintance of Madam G. when she was a nineteen year old girl. At that time she was still suffering from scrofulous glands in the neck, but was otherwise well. She had an acute rheumatism which left as sequelae edema of the ankles, loss of weight, amenorrhea, palpitation and rapid small pulse, precordial distress, and dyspnea. Even at this time there was also, however, a definite protrusion of the otherwise healthy and visually normal eyeball so that the patient slept with the eyes open, had a frightened appearance, conducted herslf in a careless and lively manner, and soon had the reputation of being a little mad.

"Coincident strumous swelling of the thyriod gland led me to suspect a similar intumescence of the cellular tissue behind the optic bulb and suggested the use of iodine and digitalis, whereupon an improvement in all her symptoms resulted . . . although she still showed an unhealthy pallor and her eyes were unnaturally wide open and prominent."

After detailing the typical symptoms of hyperthyroidism in four other cases, he concludes:

"Having given it as my opinion that the immediate cause of exophthalmos is a strumous hypertrophy of the cellur retrobulbar tissue, I wish to amplify this by saying that I regard this hypertrophy as an incidental phenomenon, secondary to an abnormal condition of the circulatory system—a blood dyserasia which, by reason of some as yet unknown scrofulous taint, takes the form of glandular growths and tissue hypertrophy."

Atypical Patent Ductus Arteriosus

The Use of a Vasopressor Agent as a Diagnostic Aid

By LAMAR E. CREVASSE, M.D., AND R. BRUCE LOGUE, M.D.

Approximately 95 per cent of patients with patent ductus have characteristic machinery murmurs. Five per cent have only systolic murmurs. In such patients, the intravenous or intramuscular administration of a pressor substance, mephentermine, may bring out a continuous murmur. This simple test is a useful adjunct in diagnosis.

IN OUR EXPERIENCE about 95 per cent of patent ducti have the typical machinery murmur, and present no problem in diagnosis. A continuous murmur maximal in the second to third left intercostal space usually means patent ductus arteriosus. Other sites usually indicate other lesions. The typical machinery murmur reflects a systolic and diastolic pressure gradient between the aorta and pulmonary artery with left-to-right shunt in both systole and diastole. The intensity of the murmur may or may not parallel the size of the ductus and the degree of shunt.

It is the atypical 5 per cent of ducti that cause difficulty in diagnosis. The diagnosis of atypical patent ductus can be most rewarding, as a seemingly hopeless and confusing situation may be resolved safely and definitely at the operating table. In atypical patent ductus there may be no murmur, a pulmonic systolic flow murmur, or a late systolic-early diastolic murmur overriding the pulmonic second sound having either a late systolic or early diastolic accentuation.[1, 2] Occasionally the murmur of pulmonary insufficiency appears with severe pulmonary hypertension. Atypical murmurs occur chiefly in infancy[3] or when secondary pulmonary hypertension develops.

When atypical murmurs are present, there are several possibilities. The ductus may be extremely small or quite large. In infants and small children with low systemic blood pressures and relatively high pressures in the pulmonary artery[4, 5] the systolic-diastolic pressure gradients may be quite small, producing turbulence of blood flow in late systole or not at all. When pulmonary hypertension complicates patent ductus, pressure gradients may be reduced or obliterated.[6] Patent ductus, when complicated by additional cardiovascular lesions, most commonly coarctation of the aorta, is usually atypical.

It becomes apparent then that size of the ductus and the pressure relationship between the aorta and the pulmonary artery[2, 6, 7] determine the type of murmur present. Following the suggestion of Bing, we have employed mephentermine sulfate (Wyamine)* in doses of 10 to 30 mg. intramuscularly and intravenously to increase cardiac output rapidly[8] and to raise aortic pressure[9] in many patients suspected of atypical patent ductus arteriosus. It produces only minor increases in pulmonary artery pressure.[9] Even in the presence of severe heart disease it safely and effectively raises aortic pressure rapidly, thereby increasing the systolic-diastolic pressure gradient between the aorta and pulmonary artery. It has a wide margin of safety, since it rarely induces serious ventricular arrhythmias.[10] However, we have observed brief bouts of bigeminal rhythm[10] at the peak of the pressor response in 2 patients, and 1 patient manifested an urticarial reaction.

The atypical murmur in infants below 1 year of age is well illustrated in a 6-month-old girl with an unexplained pulmonic systolic murmur that overrode the pulmonary second sound. After 10 mg. of mephentermine sulfate intramuscularly the typical machinery mur-

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*Kindly supplied by Wyeth Laboratories, Inc., Philadelphia, Pa.

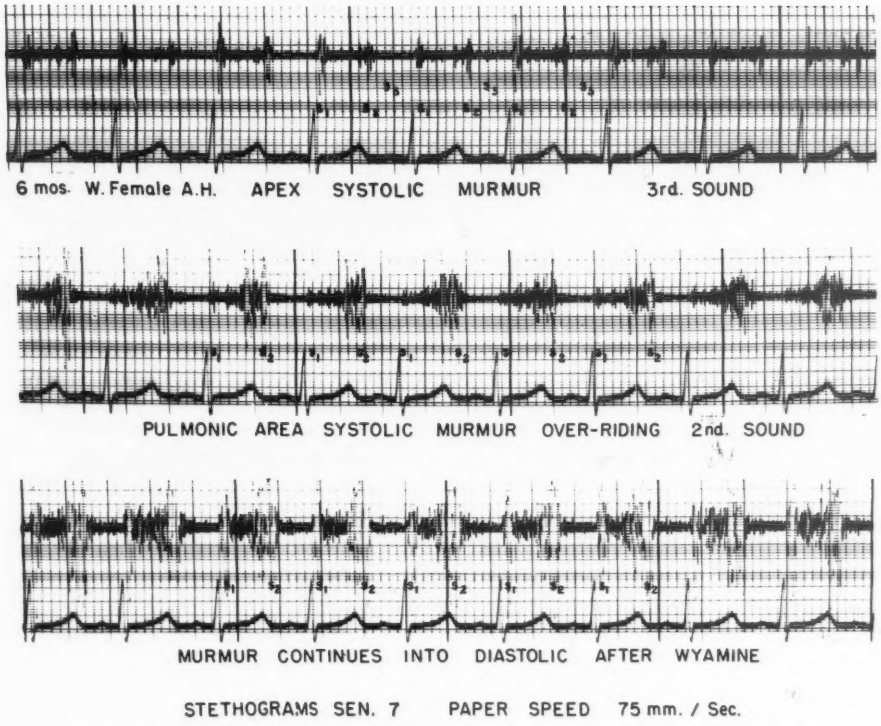

FIG. 1. Phonocardiograms and electrocardiograms showing typical murmur in a six-month-old girl.

mur of patent ductus appeared with changes in aortic pressure (fig. 1). Pulmonary artery pressures in the normal infant following birth are quite high, approximating systemic pressures.[11] With growth, pulmonary vascular resistance and pressure fall and systemic pressure rises. The typical murmur appears when both a systolic and a diastolic pressure gradient is established.

When the ductus is extremely small, there may be no murmur or only a pulmonary systolic murmur. A 4-year-old, white girl with the typical murmur of patent ductus detected earlier in childhood was referred for surgery. No murmur was audible on admission and only a faint systolic murmur appeared after vigorous exercise. After 15 mg. of mephentermine sulfate intramuscularly the typical machinery murmur appeared, and a small ductus was resected at surgery without the need of cardiac catheterization. Infants have tolerated 10 mg. of mephentermine sulfate intramuscularly without any untoward reaction; in older children 10 mg. intravenously have been well tolerated.

A 21-year-old, white woman was seen with an unexplained pulmonic-systolic murmur. It was a decrescendo blowing pulmonic-systolic murmur with a questionable early diastolic component (fig. 2, *top*). After vigorous exercise the murmur increased in magnitude but remained nondiagnostic. With rapid changes in aortic pressure, the typical continuous murmur of patent ductus appeared (fig. 2, *bottom*).

The inadequacy of exercise in bringing out the continuous murmur in atypical cases is not surprising, since exercise causes no significant change in the mean diastolic blood pressure either of patients with patent ductus

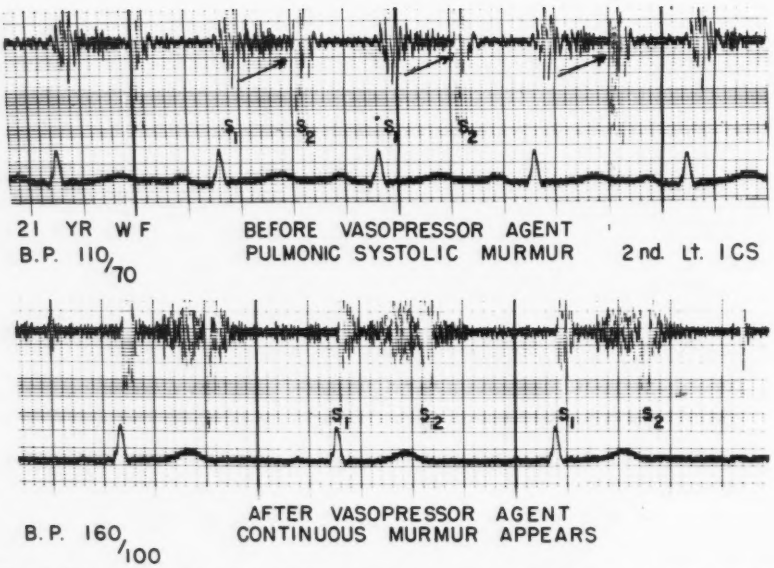

FIG. 2. Phonocardiograms and electrocardiograms showing appearance of typical continuous murmur of patent ductus arteriosus after administration of vasopressor agent. Sensitivity 5 in phonocardiograms; paper speed 75 mm./sec.

or of normal control subjects.[12] Rapid elevation in aortic systolic and diastolic pressures by a vasopressor agent increasing turbulence of flow in systole and diastole across the ductus is clearly superior to exercise in atypical cases. This magnitude of increase in the murmur and the appearance of the diastolic component is not attainable by exercise or other physiologic maneuvers (fig. 3).

In figure 4 is the phonocardiogram of a 5-year-old, Negro boy with coarctation, aortic stenosis, and heart failure. Intermittently, in the background, was a suggestion of the murmur of patent ductus. After 15 mg. of mephentermine intravenously the typical murmur of patent ductus clearly appeared (fig. 4). A large 12-mm. ductus was subsequently ligated with repair of the coarctation. There was only a 20-mm. systolic pressure gradient across the aortic valve. It is not unusual to find a "silent" patent ductus at surgery or necropsy examinations, particularly in association with coarctation of the aorta. In Abbott's autopsy series none of the 21 cases of patent ductus associated with coarctation was diagnosed clinically.[13] The ductus is usually extremely small, may communicate at or distal to the coarctation site, or may be associated with pulmonary hypertension, which accounts for its atypical nature.[14] When cardiac enlargement or heart failure is out of proportion to the clinical degree of coarctation, a large atypical patent ductus or endocardial fibroelastosis is usually present.

DISCUSSION

We have employed mephentermine sulfate in a patient with pulmonary hypertension associated with patent ductus, when a shunt could not be demonstrated by cardiac catheterization, but the murmur was demonstrated by this technic and the ductus was resected. Rapid alterations in aortic pressure by vasopressor agents should increase the left-to-right shunt in atypical patent ductus and make the shunt more readily detectable by simultaneous cardiac catheterization. We are currently investigating this problem, but clinically the appearance of the continuous murmur after vasopressor agents is so unequivocal that fur

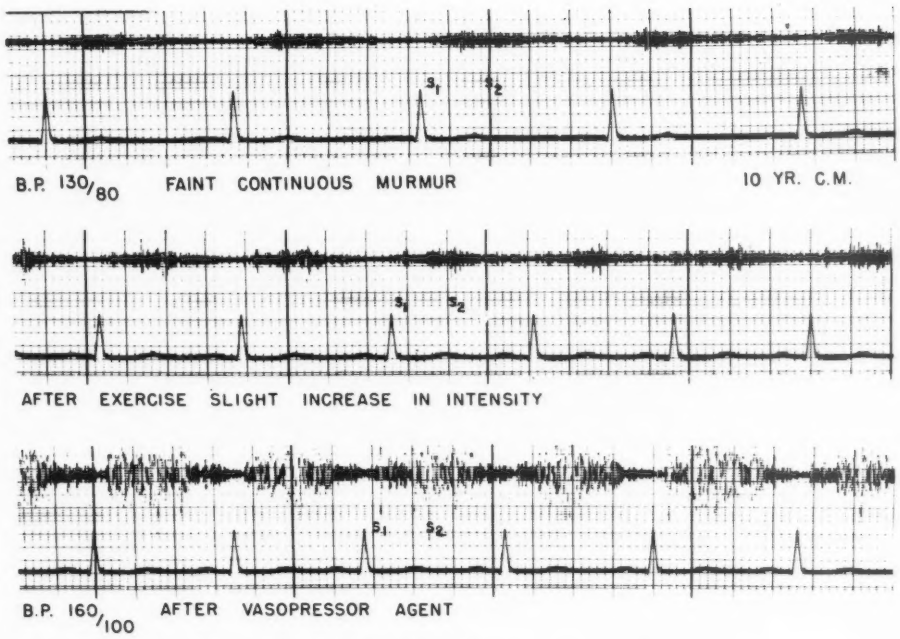

FIG. 3. Appearance of typical continuous murmur of patent ductus arteriosus after administration of vasopressor agent. Sensitivity 5 in phonocardiograms.

ther study by catheterization has not been necessary.

We have produced the typical continuous murmur by this method in approximately 12 patients with atypical murmurs that were confirmed at operation. Furthermore, we have examined the effects of mephentermine on all common congenital and acquired cardiovascular lesions[15] and the auscultatory and phonocardiographic results are quite different and not easily confused with those produced in atypical patent ductus. There have been no errors to date and the hazard, discomfort, expense, and time of cardiac catheterization have been avoided.

One can formulate the total auscultatory spectrum of this anomaly. In infants with small or absent pressure gradients no murmur, a pulmonary systolic flow murmur, or late systolic murmur overriding the second sound may be present. As the child develops, pulmonary vascular resistance falls, and systemic pressure rises, a large gradient in systole and diastole is created and the well-recognized continuous murmur appears. If the ductus is large or there are intrinsic changes in the pulmonary vessels, pulmonary hypertension may ensue. As the pulmonary artery pressure rises, the gradient lessens and reversion to atypical systolic murmurs occurs. When the pulmonary artery and aortic pressures become equal, murmurs may disappear. If the pulmonary arterial hypertension is great or the pulmonary artery dilatation distorts the pulmonic valve, the diastolic murmur of semilunar insufficiency of the pulmonic valve appears. Differential cyanosis or additional systolic murmurs appear as the pulmonary artery pressure exceeds aortic pressure and a right-to-left shunt appears. Patent ductus arteriosus associated with coaretation, or when very small or quite large, may be atypical.

Mephentermine sulfate is an effective and safe agent in rapidly raising aortic pressure

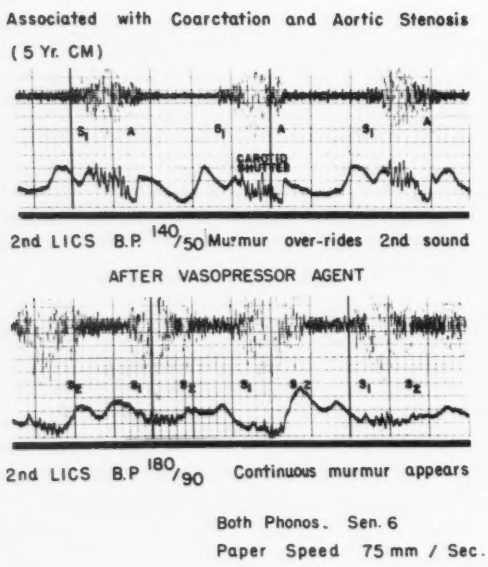

FIG. 4. Appearance of typical continuous murmur of patent ductus arteriosus after administration of vasopressor agent.

and increasing the systolic-diastolic pressure gradients between the aorta and pulmonary artery. Turbulence of blood flow in both systole and diastole is increased by this pressure alteration and the continuous murmur appears in atypical cases related to ductus size or small gradients across the ductus related to relative or of acquired hypertension in the pulmonary circuit.

SUMMARY

About 5 per cent of patients with patent ductus arteriosus have atypical murmurs. There may be no murmur, a pulmonic systolic flow murmur, or a late systolic murmur overriding the second sound. The size of the ductus and the pressure relationships between the aorta and pulmonary artery dictate the type of murmur present with this entity. Mephentermine sulfate is a safe and effective agent in rapidly raising aortic pressure and thereby creating or widening the pressure gradient between the aorta and pulmonary artery, producing the typical machinery murmur in atypical cases.

SUMMARIO IN INTERLINGUA

Circa 5 pro cento del patientes con patente ducto arteriose ha murmures de character atypic. Le murmure pote esser absente; le murmure pote esser un murmure de fluxo systolic pulmonic; o le murmure pote esser un murmure systolic tardive que rola a in le secunde sono cardiac. Le dimension del ducto e le relationes pressural inter le aorta e le arteria pulmonar determina le typo de murmure que es presente in iste entitate clinic. Sulfato de mephentermina es un salve e efficace agente pro augmentar rapidemente le pression aortic, con le resultato que un gradiente de pression inter le aorta e le arteria pulmonar es create o—si un tal es presente—accentuate e que le typic murmure de machineria es producite in le casos atypic.

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Raisz, L. G., McNeely, W. F., Saxon, L., and Rosenbaum, J. D.: The Effects of Cortisone and Hydrocortisone on Water Diuresis and Renal Function in Man. J. Clin. Invest. **36**: 767 (June), 1957.

Urine flow on a background of a maintained water load was increased during steroid administration. These effects were independent of intake and renal output of sodium. During salt restriction there was an increase in maximal urine flow and free water clearance. Sometimes the increase in water excretion was observed with a simultaneous small increase in sodium excretion. It was also noted that there was a gain in body weight and an increase in total solute excretion in some cases. The increase in glomerular filtration rate (GFR) was small after steroids and not parallel with the increase in maximal urine flow. GFR was increased by single intravenous infusions of hydrocortisone, but the increase in diuretic response to an increased intake of water was not always observed. Renal tubular water reabsorption was decreased by the steroids under consideration. It has been suggested that the additional free water is provided by a redistribution of solute reabsorption between proximal and distal tubules or by a change in tubular permeability to water.

Oppenheimer

The Growth of the Normal Aorta and of the Anastomotic Site in Infants Following Surgical Resection of Coarctation of the Aorta

By ARTHUR J. MOSS, M.D., FORREST H. ADAMS, M.D., BERNARD J. O'LOUGHLIN, M.D., PH.D., AND WILFRID J. DIXON, PH.D.

Observations were made on the growth of the anastomotic site 2 to 4 years after surgical resection of coarctation of the aorta in 5 infants who were less than 2 years of age at the time of surgery. Aortic measurements were made from biplane angiocardiograms. The physiologic adequacy of the anastomotic site was demonstrated by absence of a gradient in direct pressure measurements between the upper and lower extremities. Additional observations on the normal growth of the descending thoracic aorta were made from studies in 154 subjects with other forms of heart disease. They ranged in age from 2 days to 74 years.

IN 1945 a major milestone in the development of cardiovascular surgery was reached when Crafoord and Gross independently demonstrated that it was possible to correct coarctation of the aorta in human subjects.[1-3] Since that time aortic resection for this condition has become one of the least hazardous of present day cardiovascular surgical endeavors. Although a number of brilliant studies concerning the physiologic effects of aortic block,[4-24] the technic of repair,[25-27] the choice of suture material,[25-31] and the growth of the anastomotic site[32-37] have furthered considerably our knowledge of this condition, certain problems continue to exist.

Of particular importance in the selection of candidates for surgery is the question of growth of the suture line following aortic anastomosis. The many divergent views expressed in the literature concerning the optimal age for operative intervention attest to the significance of this issue.[30, 31, 38-64] Although this question has been studied extensively in animals, the hazards of extrapolating information obtained from animal observations are well known. This risk is especially true of problems relating to coarctation of the aorta, since, depending upon the species of animal, an appreciable difference may exist in the rate of body growth, the ultimate body size, the development of collateral circulation, the degree of vascular fragility, and the pres-

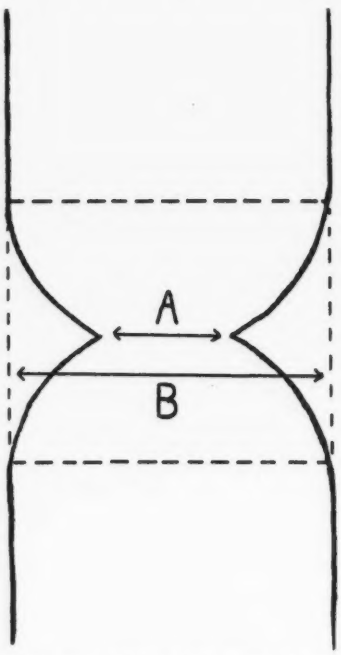

FIG. 1. Diagram showing the actual diameter (*A*) at the anastomotic site as opposed to the "expected diameter," (*B*).

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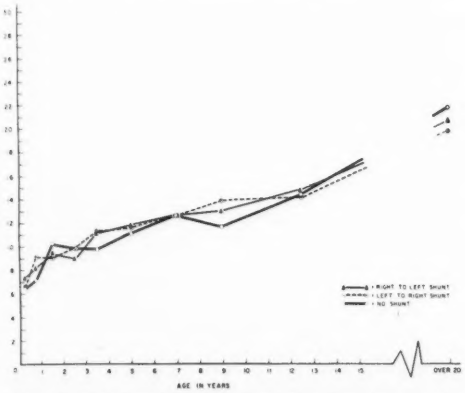

FIG. 2. Relationship of aortic diameter to age for types of physiologic abnormalities. No difference is apparent.

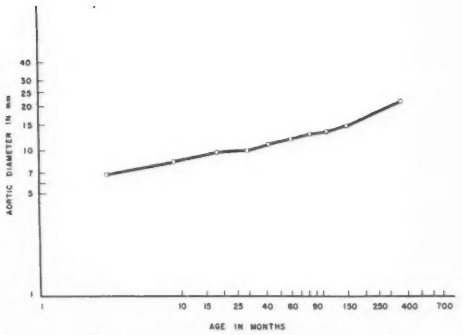

FIG. 3. Relationship of aortic diameter to age. A straight line fitted to these points has the formula $d = 3.5\ (t + 8)\ .31$ where d is the aortic diameter in millimeters and t is the age in months.

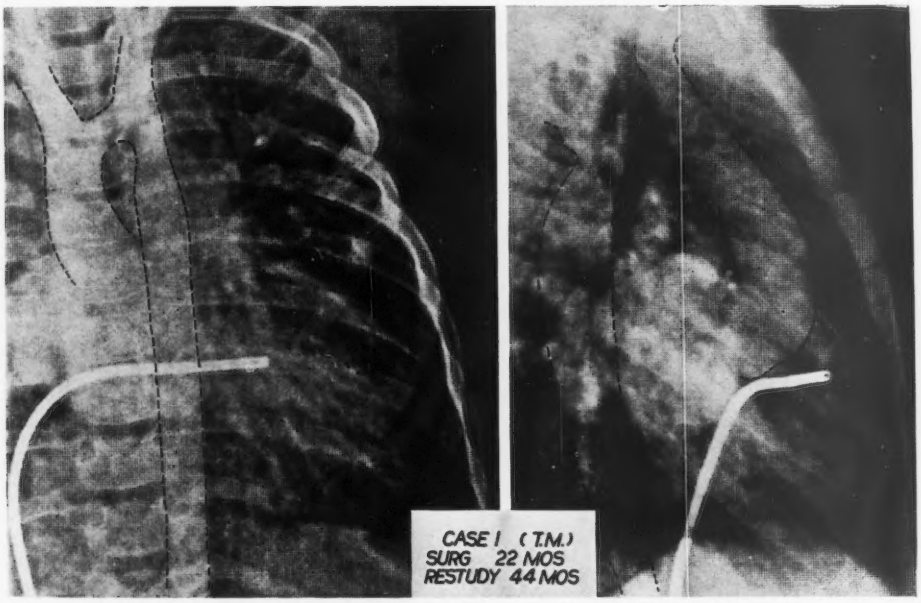

FIG. 4A. Case 1. Anteroposterior and lateral angiocardiograms after surgery.

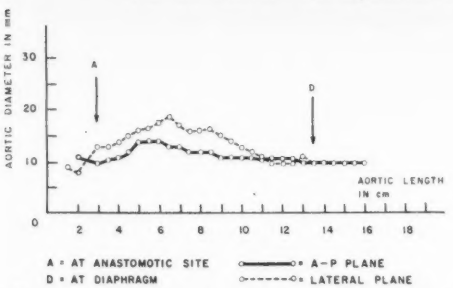

FIG. 4B. Anteroposterior and lateral diameters of the aorta in the region of the anastomosis.

sure exerted by the blood upon the aortic wall. To date no observations in man have been reported concerning the growth of aortic anastomoses or, for that matter, of the aorta itself. The present investigation was undertaken with these objectives in view.

MATERIAL AND METHODS

As a prerequisite for the critical interpretation of observations on the growth of the anastomotic site following resection of the coaretation, a pre-

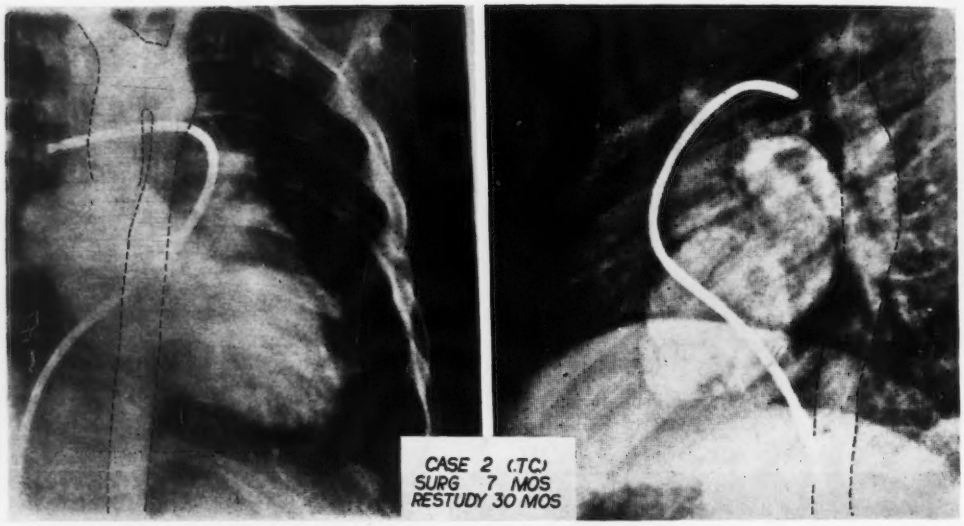

FIG. 5A. Case 2. Anteroposterior and lateral angiocardiograms after surgery.

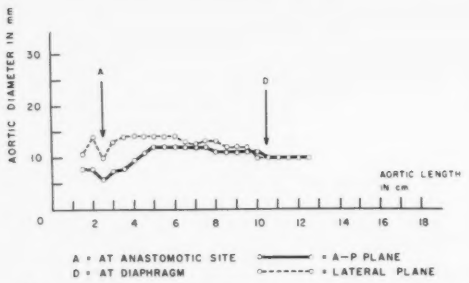

FIG. 5B. Anteroposterior and lateral diameters of the aorta in the region of the anastomosis.

liminary investigation was undertaken in which the growth of the descending aorta from birth to maturity was determined. This phase of the study consisted of recording measurements of the aortic diameter as projected on angiocardiograms in 154 patients ranging from 2 days to 74 years of age. The majority had some type of cardiovascular disorder, either congenital or acquired. The angiocardiography was of the high-speed biplane type, allowing visualization of the aorta in 2 planes as well as during both systole and diastole. However, since blood vessels are normally tubular in configuration, the diameter in only 1 plane was measured. Correction was made for distortion due to x-ray tube distance with the use of the ratio of the actual and projected size of the cardiac catheter as a basis. In each case the measurement was made with a Vernier caliper rule to the nearest millimeter at the level of the diaphragm.

The diaphragm was chosen as the level of measurement primarily because it offered a reasonably constant anatomic site. Also, it was believed that at this distance from the heart the influence of cardiac disease upon the size of the thoracic aorta would be minimal. This hypothesis was tested by classifying the patients into 3 groups, in each of which a different physiologic effect upon the size of the aorta might have been exerted: right-to-left cardiac shunt, left-to-right cardiac shunt, and no cardiac shunt. The presence or absence of a shunt was established in all cases by cardiac catheterization.

The second phase of the study consisted of observations in 5 infants who had been treated surgically for coaretation of the aorta.[5] Operation had been performed early in life because of cardiac failure or pronounced cardiomegaly. Their ages at the time of surgery ranged from 18 days to 22 months. In each case the ductus arteriosus was observed to be patent. Its mouth was located opposite the site of constriction in 2 patients (cases 2 and 3), distal to it in 2 (cases 1 and 4) and proximal to it in 1 (case 5). Aortic obstruction was limited in all subjects to the area distal to the left subclavian artery. The operation routinely consisted of aortic resection and end-to-end anastomosis with 5-0 silk suture material. The vessel ends were approximated by a continuous suture in 2 of the patients (cases 1 and 5) and an interrupted suture in 3 (cases 2, 3, and 4).

[5]Surgery was performed by Dr. J. V. Maloney, Jr. (cases 1, 2, and 4), Dr. W. H. Muller, Jr. (case 5) and Dr. William P. Longmire, Jr. (case 3).

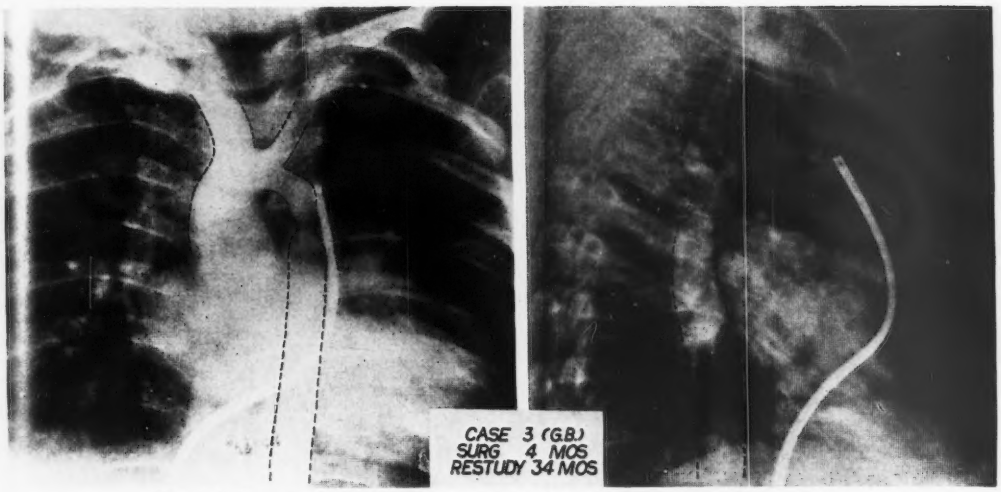

FIG. 6A. Case 3. Anteroposterior and lateral angiocardiograms after surgery.

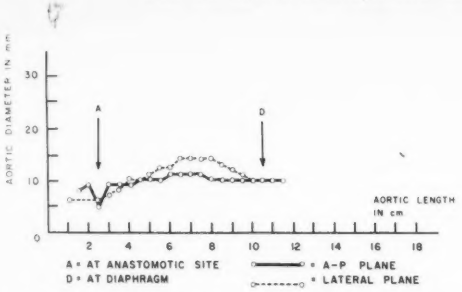

FIG. 6B. Anteroposterior and lateral diameters of the aorta in the region of the anastomosis.

All of the infants were re-evaluated approximately 2 to 4 years postoperatively. The studies at that time consisted principally of right heart catheterization, intrabrachial and intrafemoral pressure determinations, and high-speed biplane, selective angiocardiography. These were carried out with the patient in a state of basal anesthesia. The peripheral blood pressures were measured by surgically exposing a brachial and femoral artery and cannulating them with a no.-20 hypodermic needle. Two P23D Statham strain gages were used, and the impulses were recorded simultaneously by an Offner multichannel direct recorder. The measurements of the aortic lumen were made in the same manner as previously described for the normal studies. However, for this portion of the study both the anteroposterior and lateral diameters were measured, since the cylindrical form of the vessel had been altered by the effects of surgery. The average of the 2 values obtained at any given location was accepted as the inner diameter of the aorta at that particular level. Measurements were made at half centimeter intervals along the entire thoracic length of the descending portion of the vessel. By correlating the angiocardiogram with the electrocardiogram, satisfactory diameter determinations could be made during diastole as well as during systole in 2 of the patients.

The growth of the anastomotic ring was evaluated by comparing its measured diameter to the so-called "expected diameter." The latter was estimated by measuring the distance between 2 peripheral lines drawn from a point 1 cm. above the suture site to a point 1 cm. below (fig. 1). This estimate was assumed to represent the maximum intraluminal diameter that could be expected under the most favorable conditions.

RESULTS

Growth of the Descending Aorta. The aortic diameter during systole was demonstrated to be, on the average, 1.3 mm. greater than that during diastole. Therefore only the systolic measurements were analyzed. Statistical study revealed that aortic growth correlated better with age or surface area than with weight, and that surface area was slightly superior to age. However, the difference between the latter 2 was so small that, for all practical purposes, either could be used. Therefore the more familiar index of age was selected.

The influence of cardiac disease upon the diameter of the aorta at the level of the diaphragm is demonstrated in figure 2. The lack of uniformity of the relative course of the 3

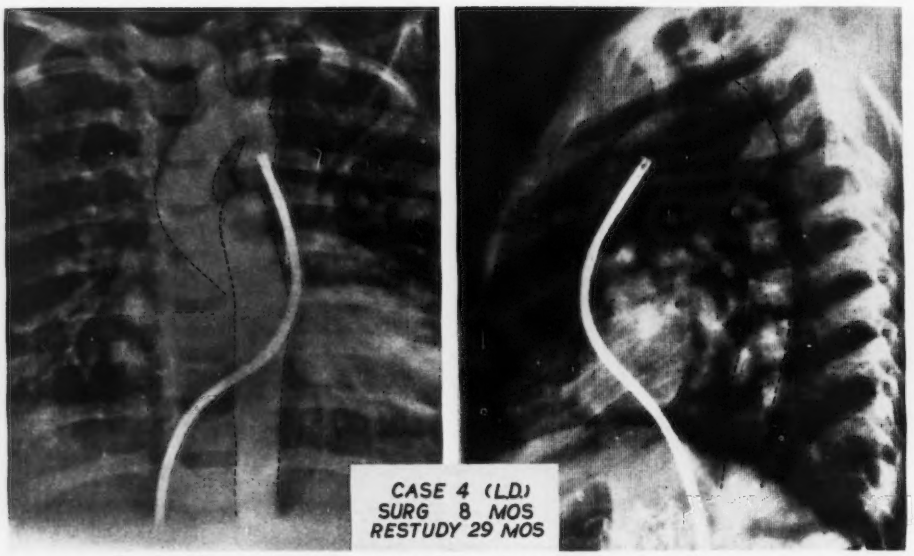

FIG. 7A. Case 4. Anteroposterior and lateral angiocardiograms after surgery.

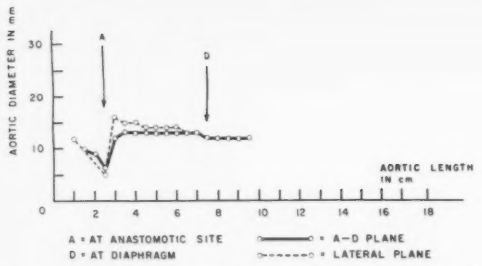

FIG. 7B. Anteroposterior and lateral diameters of the aorta in the region of the anastomosis.

curves indicates that there is no appreciable effect. The relationship of the diameter to age, irrespective, then, of cardiovascular abnormality, is presented in figure 3. In view of the foregoing, this curve may be assumed to represent the growth curve of the aorta in normal individuals. The growth curve is represented very closely by a straight line when time is computed from birth minus 8 months and both time and aortic diameter are expressed in logarithmic units. The equation for this relationship is $d = 3.5(t + 8)0.31$ where d represents the aortic diameter in millimeters and t is the age in months. This equation permits a reasonably accurate derivation of the inner diameter of the aorta at the diaphragm for any desired age.* In fact, only 5 per cent of the 154 observed cases deviated more than 45 per cent above or 30 per cent below the diameters derived, which are shown in table 1. It is to be noted that the rate of aortic growth decreases progressively with increasing age.

Growth of the Suture Line Following Aortic Resection. The angiocardiograms made in the 5 postoperative patients are reproduced in figures 4 to 8. All show evidence of poststenotic dilatation and 4 demonstrate a clearly detectable constriction at the anastomotic site, suggesting that varying degrees of growth deficit did occur. The extent of these aberrations is presented graphically for each patient. Figure 9 shows the behavior of the anastomotic ring in relation to the growth of each patient as measured by surface area. A deficiency in growth at the suture line occurred in all but 1 patient; however, the lack of a constant relationship between the anastomotic ring and body size supports the contention that the aortic diameter at the anastomotic site does not remain stationary. Additional

*The extreme right point plotted in figure 3 is somewhat arbitrarily located at 400 months and represents all patients over the age of 15 years.

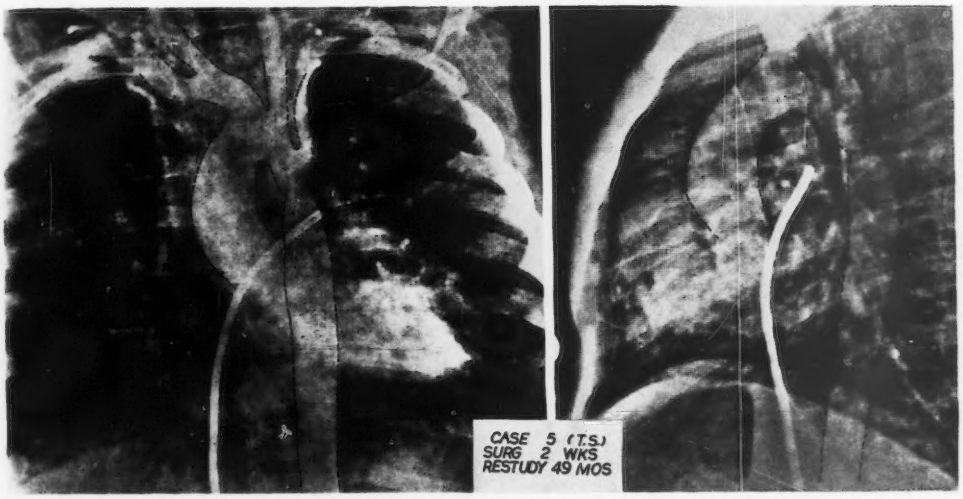

FIG. 8A. Case 5. Anteroposterior and lateral angiocardiograms after surgery.

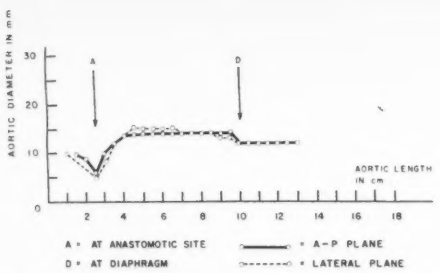

FIG. 8B. Anteroposterior and lateral diameters of the aorta in the region of the anastomosis.

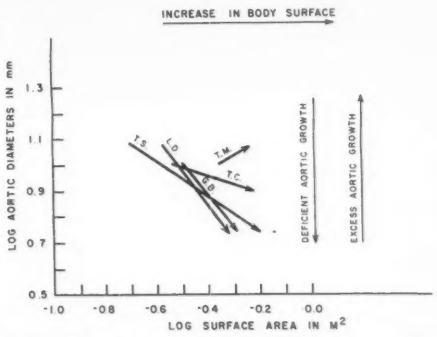

FIG. 9. Graph showing relationship of aortic diameter at anastomotic site to body growth. Since no measurements were made at surgery, the aortic diameter at the diaphragm was selected as the base line.

evidence for this conclusion is the finding in the 2 patients (cases 4 and 5) that the diameter was 1 mm. larger in systole than in diastole, indicating that the anastomotic ring is distensible. In table 2 the degree of growth retardation is quantitatively expressed as the percentage of the "expected diameter"; in no case was this less than 55 per cent.

Hemodynamic Effects of Various Degrees of Aortic Obstruction. Results of the physiologic studies made in the 5 surgically treated infants are presented in table 3. In the 4 whom comparative measurements were made of blood pressures of upper and lower extremities, the relationships were normal. An incidental finding was the presence of pulmonary hypertension, which occurred in various degrees of severity in 4 patients. The 1 patient in whom it was most pronounced was discovered to have an interventricular septal defect.

The pulse propagation times and the brachial and femoral intra-arterial pressure ratios are presented in table 3. These figures were well enough within the normal range to preclude functional obstruction of the aorta. The values in the table representing the normal range were compiled from data published by other investigators.[7, 11–13, 65, 66]

TABLE 1.—*Computed Average Normal Diameter of the Aorta at the Level of the Diaphragm for Various Ages*

Age (yrs.)	Diameter (mm.)
Birth	6.8
1/12	6.9
2/12	7.2
3/12	7.4
4/12	7.6
5/12	7.8
6/12	8.1
7/12	8.3
8/12	8.3
9/12	8.5
10/12	8.7
11/12	8.9
1	8.9
2	10.5
3	11.5
4	12.3
5	13.2
6	13.8
7	14.4
8	15.1
9	15.5
10	15.8
11	16.6
12	17.0
13	17.4
14	17.8
15	17.8
Over 15	20.9

TABLE 2.—*Diameter Measurements and Estimated Growth of the Suture Line Following Aortic Resection and End-to-End Anastomosis*

Case	Age at surgery (mos.)	Interval since surgery (mos.)	Diameter at suture line (mm.)	Expected diameter (mm.)	Growth attained
1	22	22	11.5	11.5	100
2	4	30	8.0	9.5	84
3	7	23	5.5	7.5	73
4	8	21	5.5	10.0	55
5	1/2	49	5.5	10.0	55

*Expressed as percentage of expected diameter.

DISCUSSION

The observations reported here suggest that growth of the suture line following aortic anastomosis in infants is frequently deficient. However, the data also indicate that the anastomotic ring is readily distensible and therefore probably capable of future growth. It is probable, then, that the suture site does not remain absolutely stationary. Experimental evidence recorded in the literature favors this view.[29, 30, 33, 35]

Results of the present study permit some interesting speculation concerning the optimal age for surgery. It was found, for example, that from birth to maturity the diameter of the descending aorta undergoes about a 3-fold increase. The growth increment proceeds at a more rapid rate earlier in life than later, so that at 3 years of age the diameter is about 55 per cent of that in an adult. It has

TABLE 3.—*Postoperative Hemodynamic Data in Five Patients Following Surgery*

Case	Age at surgery (mos.)	Months since surgery	Blood pressure (mm. Hg) Intrabrachial	Intrafemoral	Ratios femoral : brachial Systolic pressure	Pulse pressure	Delay in onset of femoral pulse* (sec.)	Build-up time of femoral pulse (sec.)	Evidence of shunt	Pulmonary hypertension (mm. Hg)
1	22	22	——	121/80				0.13	+†	+75/17
2	4	30	100/65	102/62	1.02	1.14	0.0	0.16	—	+36/21
3	7	23	120/93	123/75	1.03	1.78	0.01	0.16	—	+42/18
4	8	21	129/66	129/79	1.00	0.79	0.0	0.16	—	+50/25
5	1/2	49	94/64	96/64	1.02	1.07	0.0	0.14	—	—
Range of normal					0.91-1.06	0.82-1.20	—0.01-+0.02	0.13-0.18		

*Interval between onset of upstroke of brachial pulse and onset of upstroke of femoral pulse wave.

†Interventricular septal defect.

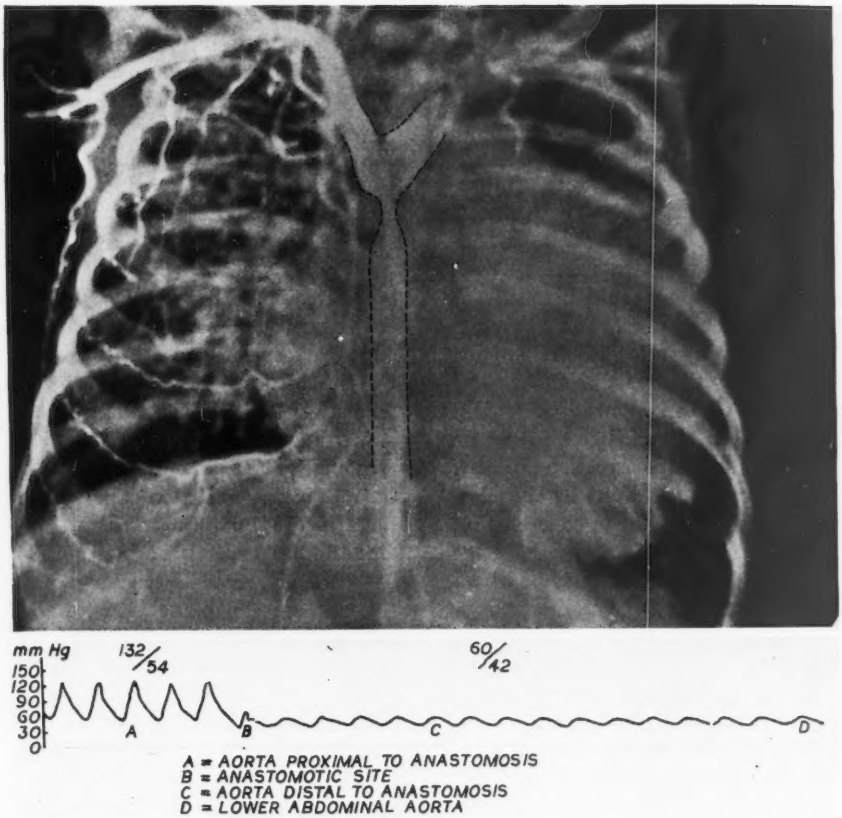

FIG. 10. Aortogram and aortic blood pressure withdrawal tracing obtained in an 8-week-old infant who had been treated surgically at the age of 2 weeks for coaretation of the aorta. The patient had a significant degree of anatomic and physiologic obstruction, suggesting that the aortic lumen had not been completely restored at surgery.

been demonstrated in dogs that the passage of blood through a stenotic orifice is not interfered with unless the intraluminal diameter is reduced to about 50 per cent.[67] That this figure probably applies to man also is suggested by the absence of physiologic evidence of aortic obstruction in our studies, even though the diameter was reduced to 55 per cent of the "expected diameter." On the basis of these limited observations, then, it would appear that after 3 years of age the risk is indeed slight of recurrence of aortic constriction of a significant degree. The earlier the anastomosis is performed prior to this age the greater is the amount of aortic growth that is required to ensure an adequate lumen. Even at the age of 1 month, however, retardation of future growth would have to exceed 65 per cent to result in a physiologically significant obstruction.

In deriving these conclusions, 2 basic principles are taken for granted: that the surgeon completely excise the constricted area and that the lumen of the vessel not be compressed in creating the anastomosis. The significance of these prerequisites is reflected in the data presented in figure 10. The patient was an infant who at the age of 2 weeks had been treated surgically for coaretation of the aorta with excellent clinical results. At the time

of restudy, however, only 6 weeks later, the anastomotic diameter was but 35 per cent of the "expected diameter" and there was physiologic evidence of severe aortic obstruction. The aortic lumen obviously had not been completely restored at the time of surgery.

The demonstration of an elevated pulmonary artery pressure in 4 of the 5 subjects studied postoperatively merits some discussion. Only 1 of these patients had an associated malformation that could account for this finding. Although the occasional development of pulmonary hypertension in patients with coaretation of the aorta and a patent ductus arteriosus is well known,[18, 60, 61, 68–71] no studies have been reported concerning its fate following surgical correction of the underlying abnormalities. It is of considerable interest as well as of some concern that we found pulmonary hypertension of some degree as long as 2 to 3 years after operation.

Summary

Observations were made in 5 infants on the growth of the anastomotic site approximately 2 to 4 years after surgical correction of coarctation of the aorta. At the time of surgery, 4 patients were under 9 months of age, the youngest being 18 days and the oldest being 22 months. Observations were also made on 154 subjects from 2 days to 74 years of age to establish the average normal growth of the descending aorta. Systolic and diastolic measurements were made from biplane angiocardiograms in both groups. In the postoperative patients the physiologic adequacy of the suture site was determined by intra-arterial blood pressure and pulse measurements.

These studies demonstrate that from birth to maturity the diameter of the aorta at the level of the diaphragm increases about 3-fold. At 3 years of age it is about 55 per cent that of an adult. In the subjects studied postoperatively, anatomic stenosis of the aorta occurred in 4, but no physiologic obstruction could be demonstrated.

Since physiologic obstruction was not apparent with an aortic diameter of 55 per cent of the expected normal and since the average diameter in children 3 years of age is abou 55 per cent that of an adult, it was conclude that anastomoses performed at this age shoul remain functionally patent regardless of fu ture growth. Even if surgery were performe at 1 month of age, retardation of growt would have to exceed 65 per cent to result i a physiologically significant obstruction.

Summario in Interlingua

Esseva facite observationes in 5 infante con respecto al crescentia del sito anastomoti approximativemente 2 a 4 annos post le co rection chirurgic de coarctation del aorta. Al tempore del operation, 4 del patientes habev minus que 9 menses de etate. Le etate de plus juvene esseva 18 dies, illo del plus avan tiate 22 menses. Esseva etiam facite observa tiones in 154 subjectos de etates de inter 2 dies e 74 annos pro establir le normal crescen tia medie del aorta descendente. Mesurationes systolic e diastolic esseva facite ab angiocar diogrammas biplan in ambe gruppos. In le patientes postoperatori, le adequatia physio logic del suturas esseva determinate per mesu rationes del pulso e del tension de sanguine intra-arterial.

Iste studios demonstra que ab le nascentia usque al maturitate le diametro del aorta al nivello del diaphragma es augmentate circa triplemente. Al etate de 3 annos, illo es circa 55 pro cento de illo de un adulto. Inter le subjectos studiate post le operation, 4 mon strava stenosis anatomic del aorta, sed nulle obstruction physiologic poteva esser identifi cate.

Viste que nulle obstruction physiologic es seva apparente quando le diametro aorti amontava a solmente 55 pro cento del expec tate valor normal e viste que le diametro medie in juveniles de 3 annos de etate e circa 55 pro cento de illo trovate in adulto il esseva concludite que anastomoses effectu ate a iste etate remane functionalmente pa tente, sin reguardo al crescentia futur. Me mo si le operation es effectuate al etate de mense, le retardation del crescentia futur del exceder 65 pro cento pro resultar in un ob struction de signification physiologic.

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Pre-Harveian Doubts of Galenic Doctrine

In the course of his description and after remarking that the right ventricle of the heart transmits its blood to the left ventricle, he adds, "not through the middle wall of the heart, as is commonly believed, but by a very ingenious arrangement . . . . by a long course through the lungs." This, Servetus remarks, represents "a truth which was unknown to Galen." This statement is correct if by it we understand Servetus to refer merely to a difference in emphasis, since Galen had, in fact, presented the fundamental information necessary for the discovery and description. Here let us remember that Servetus has revealed himself as a confirmed and literal student of Galen.—CHARLES D. O'MALLEY. *The Complementary Careers of Michael Servetus: Theologian and Physician.* History of Medicine and Allied Sciences. **8**: 387, 1953.

So-Called Primary Venous Obstruction in the Upper Extremity

Paget-Schroetter Syndrome

By JOHN T. PHELAN, M.D., AND CHARLES W. CRUMPTON, M.D.

A case is reported of primary venous obstruction in the upper extremity, the Paget-Schroetter syndrome. The literature of this unusual condition is reviewed and the mechanism of its development and its treatment is discussed.

VENOUS OBSTRUCTION in the upper extremity is not commonly encountered clinically, and when it does occur it is usually associated with metastatic carcinoma involving the axilla, or from pressure due to mediastinal or lung tumors. A number of cases have been documented in the medical literature where venous obstruction has occurred in the absence of these contributing factors and, as such, a variety of synonyms, such as "effort," "strain," or "traumatic" thrombosis of the axillary or subclavian vein, or of both, have been used to describe it. In addition, Hughes[1] has suggested the term "Paget-Schroetter's syndrome" after the two physicians who first described this condition as a clinical entity. More recently, Lord and Rosati[2] have employed the term "neurovascular compression syndrome of the upper extremity" to indicate abnormal anatomic compression of the axillary and subclavian vessels and associated nerves, irrespective of whether these structures were involved singly or in combination. However, when venous obstruction per se is the principal clinical picture, we prefer the term "Paget-Schroetter syndrome."

Because this condition has received but little attention in the medical literature, it is the purpose of this paper to present a case report of the Paget-Schroetter syndrome recently observed at our hospital and to review the literature related to its etiology, diagnosis, treatment, and prognosis.

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CASE REPORT

The patient, a 23-year-old white man, was first seen for persistent swelling of his right arm. He stated that 3 months previously he noted a sudden swelling of his right upper extremity, associated with mild pain, heaviness, and discoloration of the entire limb. He was not unduly incapacitated and continued to work as a machine operator. In operating the machine, he was required to abduct the right arm to about 160°, and then forcibly push a switch about every 4 minutes. He had been employed at this type of work for about 3 years prior to the onset of his present illness.

On physical examination, the right upper extremity was grossly enlarged when compared with the left arm; definite dilatation of the superficial veins of the right hand, forearm, and upper arm was noted; and slight, but definite, visible cyanosis of the involved extremity was also observed. Palpation was not remarkable, and pitting edema was absent. The circumference of the right forearm was 2 inches greater than the left; the mid-upper arm was 1½ inches greater than its left counterpart. Arm, shoulder, and hand motions were within the normal range. The remainder of the physical examination was negative.

Routine blood studies, coagulation time, prothrombin-time determination, and urinalysis were normal. Roentgenograms of the chest, shoulder, and cervical vertebrae were reported as negative. The venous pressure in the right arm was 60 cm. higher than the left arm. Figure 1 shows an axillary venogram.

Conservative measures were employed in the treatment of this patient, and in 2 weeks temporary improvement was noted. The patient, however, refused surgical treatment.

REVIEW OF THE LITERATURE

Clinical Findings. As in our case, the majority of patients described with this condition have been men between the ages of 2[illegible] to 25 years. In addition, the right arm ha[illegible]

n involved more frequently than the left l, according to Hughes,[1] this phenomenon not related to the right-handed predominnce of the general population.

The signs and symptoms of this syndrome usually quite characteristic and, in most llected cases, sudden nonedematous swelling, discoloration, pain, and prominent cutaous veins of the involved arm have been ted. In most patients some unusual form muscular exercise has preceded the onset symptoms. In addition, the venous pressure the involved arm has been reported as elevated, principally following exercise. Infrared ray photography has demonstrated an increased collateral venous circulation of the involved limb, particularly over the upper arm and anterior chest wall. Furthermore, a number of authors have shown by venography nonvisualization of the axillary vein, suggesting this vein to be the principal site of obstruction.[3-5] Others, however,[6, 7] have described the area of obstruction at the subclavian vein level and, in some instances, normal venograms have been described.[8]

Etiology. The underlying mechanism for the venous obstruction has been the subject of many reports. Earlier writers[9] stressed the importance of syphilitic infection; however, it is now considered of little importance. Most authors have directed their attention to the anatomy of the axillary and subclavian veins, with particular interest given to possible sites of compression by contiguous bony and soft-tissue structures.

Lowenstein,[10] in 1924, following a detailed anatomic study of the shoulder region found the axillary vein to be compressed by the costocoracoid ligament and subclavius muscle, when the arm assumed a position of hyperabduction and lateral rotation. He suggested that compression of the axillary vein by this maneuver injured the endothelium and thus introduced a site for thrombus formation. Furthermore, he considered the venous stasis that occurred during periods of muscular exertion to be an important contributing factor. It is of interest that Lord and Rosati[2] in a recent paper emphasized that this area is a frequent point of obstruction to the axillary vein.

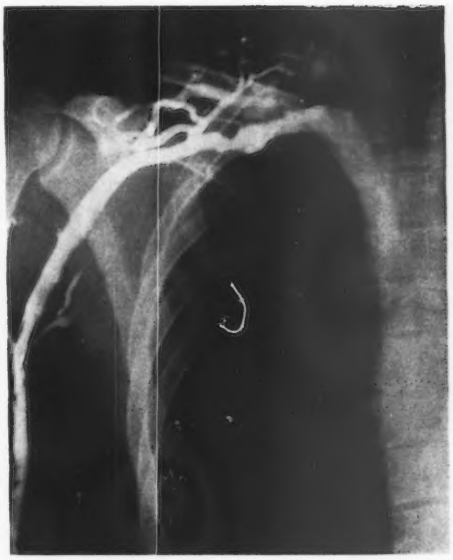

FIG. 1. Venogram of the case presented, showing the point of axillary vein obstruction as manifested by the V-shaped notch. On close inspection actual streaming of the radiopaque dye is to be noted.

Gould and Patey[11] concluded from their anatomic investigation that a sudden contraction of the subclavius muscle compressed the axillary vein, rupturing the delicate underlying intraluminal subclavia-axillary valve and thereby providing a nidus for the development of a thrombus. These authors also stressed the importance of venous stasis as a predisposing factor.

Another possible explanation has been advanced by Veal and McFetridge,[12] who showed by venographic examination that compression of the axillary vein by the subscapularis muscle and head of the humerus occurred when the arm assumed the position of hyperabduction. Wright,[13] however, demonstrated by anatomic dissection that the arm in hyperabduction stretched and compressed the axillary and subclavian vein at two sites: the interspace between the first rib and clavicle and at the origin of the pectoralis minor muscle and coracoid process.

Falconer and Weddel,[14] have indicated that hyperabduction of the arm is not the only motion of the shoulder girdle that leads to compression of the vessels and nerves that pass between the first rib and clavicle. They have shown that backward and downward bracing of the shoulders, and hyperextension of the neck, narrows this space sufficiently to compress the underlying artery, vein, and accompanying nerves.

Sampson, Sanders, and Capp,[15] from a study of patients with prominent arm and chest veins, concluded that this condition was observed principally in deep, broad-chested individuals with soldier-like postures. Furthermore, their patients presented radiographic evidence of prominent first ribs that projected laterally and anteriorly, in conjunction with upward- and backward-directed clavicles. Under these conditions, the space between the first rib, clavicle, and subclavius muscle is sufficiently narrowed to cause compression of the subclavian vein. Sampson[16] has described cases of the Paget-Schroetter syndrome that illustrated this factor.

More recently, McCleery and his co-workers[17] have described obstruction of the subclavian vein principally in the area bounded by the scalenus anticus muscle posteriorly, the subclavius muscle and clavicle anteriorly, and the first rib inferiorly. They refer aptly to this area as the "bottleneck" and have described in detail the technic for exploring this region.

A unique hypothesis has been presented by Hughes,[18] who has suggested that an abnormally placed phrenic nerve, i.e., one that passes posteriorly to the subclavian vein, may be the underlying mechanism. He has postulated that increased diaphragmatic excursions that accompany muscular exertion tense the phrenic nerve which, in turn, compresses the subclavian vein against the adjacent medial border of the scalenus anticus muscle. He has indicated that the taut, bow-string-like action of the phrenic nerve may act as a ligature. Such a theory, he believes, could explain the absence of emboli and reported negative exploratory findings in some of the published case reports.

Less common etiologic factors have been implicated as possible sites of vein compression, namely, bony lesions of the clavicle and complications following fracture of this bone. However, these conditions appear to involve the entire neurovascular bundle rather than the vein per se.[2] The theory of venous spasm has been emphasized by Ochsner, DeBakey and others.[19,20] However, this mechanism would appear to be a complication of the venous obstruction rather than an etiologic factor.

Although considerable emphasis has been directed to the scalenus anticus muscle, with an associated cervical rib, as the underlying mechanism for neuroarterial complications arising from this area, Hughes collected only a few reports where a cervical rib has been found in association with the Paget-Schroetter syndrome.

Prognosis. The prognosis for patients with this condition is difficult to evaluate. Hughes[1] has reported that the majority of patients recover in time; however, slight edema, cyanosis, and prominent cutaneous veins may persist, although they seldom cause any great degree of discomfort. He states that pulmonary emboli are rarely, if ever, encountered, and no death has occurred from this entity. Nevertheless, a number of documented cases have been published where symptoms have been severe and disabling. In this regard, Kleinsasser[21] has reported that 75 per cent of patients with the Paget-Schroetter syndrome have some residual effects.

Treatment. The treatment of this condition is far from standardized. Almost all the authors stress the importance of minimizing the formation of edema by elevation and rest of the arm. Hughes has suggested anticoagulant therapy to limit the propagation of the thrombus and reduce the degree of venous obstruction, and Jones[22] believes that caution should be exercised in permitting the patient to return to their usual form of occupation, especially if the mode of employment appears responsible.

McCleery and others[2, 17] have suggested surgical exploration of the axillary and subclavian vein. In their patients obstruction

axillary or subclavian veins was extravascular in nature, and relief of symptoms was prompt following its relief. According to Hughes, surgical removal of the thrombus has been described and, in some instances, favorable results have been obtained. Additional surgical measures have been reported, namely, cervical sympathectomy[19, 20] and excision of the obstructed vein segment.[23] In each instance, alleviation of symptoms has been reported; however, the cases that have been treated in this manner have been few in number.

Discussion

From this account it will be seen that the current tendency is to attribute the underlying mechanism of the Paget-Schroetter syndrome to direct interference with the venous flow of the arm (with or without thrombus formation) by extravascular compression of the axillary or subclavian vein. It is also clear that the anatomic site responsible for the venous compression may be variable, a point that requires emphasis, particularly if surgical intervention is decided upon.

The treatment of this condition has been primarily conservative in nature and not unlike that employed for deep venous obstruction of the lower extremity. If our concept regarding this type of venous obstruction is correct, it would seem reasonable to advocate early surgical intervention to remove the extravascular venous obstruction and the axillary or subclavian venous thrombus, if present. Anticoagulant therapy would also appear to be an additional useful therapeutic measure.

However, as the majority of cases are observed days after the onset of symptoms, the fact remains that a venous thrombus, if present, would be so organized as to preclude its surgical removal. Under such conditions, a reasonable course of conservative therapy would seem advisable, with attention directed to methods of controlling edema and avoiding motions of the arm that initiated the process. If symptoms persist, surgical exploration of the infraclavicular and supraclavicular spaces should be performed with the idea of removing the source of the venous compression. However, it should be done with the full understanding that the venous compression point may be variable and, as such, a thorough exploration of the axillary and subclavian veins is necessary. Even though the most consistent site of venous obstruction appears to be the region where the axillary vein passes between the costocoracoid ligament, the subclavius muscle and the first rib, a diligent search must be made for additional compression points that have been described.

Summary

A case report of the Paget-Schroetter syndrome and a review of the literature pertaining to this subject have been presented. This condition represents extravascular obstruction to the axillary or subclavian vein, or both, with or without thrombosis, by adjacent bone and soft-tissue structures. The treatment of this syndrome has been primarily conservative in nature; however, it would appear that early operative intervention with the purpose of removing the extravascular obstruction and re-establishing venous flow by a surgical phlebotomy, when necessary, is the procedure of choice.

Summario in Interlingua

Es presentate le reporto de un caso de syndrome de Paget-Schroetter e un revista del litteratura concernite con iste thema. Il se tracta de un condition in que obstruction extravascular del vena axillar o del vena subclavian o de ambes (con o sin thrombosis) es effectuate per adjacente structuras de osso e de histos molle. Usque nunc le tractamento de iste syndrome ha essite primarimente de natura conservative, sed il pare que le manovra de election deberea esser plus tosto un prompte intervention chirurgic serviente le objectivo de eliminar le obstruction extravascular e de restablir le fluxo venose, si necessari, per phlebotomia.

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While increased serum transaminase levels within 6 hours to 4 days after the onset of the infarct were found most commonly in conjunction with acute myocardial infarction, elevated levels even to the extent of 500 units were found often enough in necrosis and infarction of other organs to suggest caution in interpretation. Curves of the same configuration as that obtained with myocardial infarction were obtained in other situations as was illustrated in patients with multiple infarctions, particularly pulmonary infarctions.

Wendkos

Effects of Chlorothiazide on Specific Renal Functions in Hypertension

By A. C. Corcoran, M.D., Cathel Macleod, M.D., Harriet P. Dustan, M.D., and Irvine H. Page, M.D.

Oral administration of chlorothiazide depresses glomerular filtration, increases blood urea, maintains sodium output in the face of decreased filtered sodium load, and paradoxically for a diuretic, in these and in tests done shortly after intravenous administration, increases the efficiency of water reabsorption.

A PREVIOUS report on the mechanism of action of chlorothiazide[1] was based on observations on hemodynamic functions. Studies of specific renal functions were done concurrently in some of the patients and in others that were treated identically, except for the omission of some of the hemodynamic observations.

The results show that, in addition to its recognized saluretic and kaluretic properties,[2] chlorothiazide in therapeutic doses may depress glomerular filtration, may increase blood urea, and causes a paradoxical increase in "osmotic ceiling."

Methods

Renal effects of chlorothiazide* were studied in 15 patients. Eleven were given the drug in a dose of 1 Gm. twice daily for periods of 3 to 14 days. Their renal functions were measured before and at the end of the course. Renal function was tested in 4 patients just before and again 1 hour after the intravenous injection of 0.5 Gm. of this agent.

Renal plasma clearances of p-aminohippurate (C_{PAH}) and mannitol (C_M), and water and electrolyte outputs were measured by methods previously described.[3] It is assumed that C_{PAH} is equivalent to effective renal plasma flow, and C_M times 1.1 (to correct for possible mannitol reabsorption or storage) is equivalent to glomerular filtration rate. Tests were done during osmotic (mannitol) diuresis in 6 patients, in the prolonged and in all in the acute study; these conditions enabled measurements of stable excretion rates of electrolytes and calculation of tubular reabsorption of osmotically "free" water ($T^c_{H_2O}$). This function is an index of relative osmotic ceiling.[4] The stimulus to water reabsorption was either fluid deprivation (4 cases) or intravenous infusion of Pitressin (6 cases). All functions are expressed in units per minute relative to 1.73 $M.^2$ body surface area.

Brachial arterial pressure was determined by auscultation during the tests. Ten of the 11 patients in the prolonged study were weighed daily on awakening. Supine and standing arterial pressures were measured 4 times daily in 8 patients undergoing the prolonged study. Five of the 11 patients receiving oral and 3 of the 4 given intravenous chlorothiazide continued treatment with the antihypertensive drugs which they had taken for many months.

Results

Prolonged Administration

Renal Hemodynamics. During the control periods C_{PAH} ranged from 128 to 401 ml. Administration of chlorothiazide did not change effective renal plasma flow in 6 patients and was followed by slight decreases in 4 (table 1). Control levels of glomerular filtration rate ranged from 43 to 168 ml. in 11 and uniformly decreased during treatment with chlorothiazide (mean −29 per cent, range −16 to −50). Arterial pressure decreased at the time of the chlorothiazide clearance study in 5 patients; 4 of these demonstrated decreased renal vascular resistance and 1 an increase. Among the 5 showing no change in arterial pressure, renal vascular resistance decreased in 3 and was unchanged in 2. (Filtration fraction was decreased in all.)

Electrolyte and Water Excretions. These functions were studied during osmotic diuresis in 6 patients (table 2). During chloro-

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*Kindly supplied by Dr. John R. Beem, Merck Sharp & Dohme.

TABLE 1.—*Renal Hemodynamic Effects of Chlorothiazide**

Patient no.	Study	C_{PAH} (ml./min./1.73 M.²)	$C_M \times 1.1$	FF	MBP (mm. Hg)	R (dynes/sec./cm.$^{-5}\times10^3$)	Blood urea (mg. %)	Hematocrit (ml. %)	Body weight (lbs.)	Blood pressure average (mm.Hg) Supine	Standing
8	C		156		123			38	154	177/114	145/108
	D		95		124			42	149	153/104	130/99
9	C	238	78	.33	168	28.4	46	44	163	243/135	235/132
	D	206	62	.30	161	32.9	39	44	160	235/127	213/127
10	C	289	83	.29	162	25.23	36	40	213	195/135	160/118
	D	305	58	.19	133	17.9	55	44	210	169/125	161/127
	C†	365	120	.33	146	18.6	38	37	206		
	D†	330	67	.20	120	16.5	43	38	200		
11	D	510	98	.19	136	11.4	39	42	227	151/101	146/108
	C	550	130	.24	147	12.1	30	39	224	181/123	182/134
	D	505	86	.17	105	8.8	43	42	220‡		
12	C	129	43	.33	152	52.3	85	40	120		
	D	128	36	.28	150	50.2	94	42	116		
13	C‡	497	104	.20	119	9.3	19	47	195	160/100	143/93
	D	377	68	.18	103	10.1	36	49	187	138/86	108/76
14	C‡	304	78	.26	123	17.4	28	41	110	163/100	148/103
	D	320	57	.18	105	12.5	40	47	105	135/90	103/80
15	C‡	175	65	.37	157	38.4		43			
	D	143	47	.33	160	45.3		46			
16	C‡	560	157	.24	129	10.0	26	41	178	163/110	155/116
	D	558	117	.21	117	7.3	27	52	174	133/94	121/92
17	C‡	620	168	.24	116	8.4	33	39	165	169/106	148/104
	D	453	84	.19	122	10.6	47	46	162	142/97	123/89
18	C‡	424	98	.23	125	11.4		47	191		
	D	402	82	.20	122	11.8		47	186		
Means	C	379	105	.27	138	22.8	38	42	174	182/115	165/113
	D	339	72	.22	127	20.7	46	46	170	157/103	138/100
Percentile changes		—10	—29	—19	—8	—9	+21	+9.5	—2.2	—14/—10	—16/—12

*C_{PAH}, PAH clearance. $C_M \times 1.1$, glomerular filtration rate. FF, filtration fraction. R, renal resistance. Hematocrit, venous hematocrit. C, control observations. D, chlorothiazide observations.

†Done during hydralazine administration.

‡Done during osmotic diuresis.

thiazide administration, glomerular filtration rate was depressed in all and osmolar clearance (C_{Osm}) in 5. The absolute rate of tubular reabsorption of osmotically free water ($T^c_{H_2O}$) was decreased in 4 patients and increased in 2 who had received the drug for no more than 3 days. When this function was calculated in relation to simultaneously measured glomerular filtration rate ($T^c_{H_2O}/C_M \times 1.1$) 100, the relative rate was found to be increased in 5 of 6 cases, the exception being the patient with the lowest initial glomerular filtration rate. Filtered sodium (L_{Na}) load, the product of glomerular filtration rate times serum sodium, was consistently decreased, as was the rate of sodium excretion ($U_{Na}V$). However, the percentage of filtered sodium that was reabsorbed ($L_{Na}-U_{Na}V/L_{Na}$ 100 was unchanged or, in 1 case, increased. Potassium clearances were increased in 4 patients in whom this function was measured.

Other Observations. All patients lost weight during treatment. Venous hematocrit ratio rose slightly in all but 1. Serum

TABLE 2.—*Electrolyte and Water Excretion during Osmotic Diuresis before and after Chlorothiazide**

ient no.	Study	V (ml./min./ 1.73 M.²)	$U_{O_{sm}}$ (mOsm./L.)	$C_{O_{sm}}$ (ml./min.)	Tc_{H_2O} (ml./min.)	$Tc_{H_2O}/C_{Man} \times 100$	L_{Na} (mEq./min.)	U_{NaV} (mEq./min.)	% Na reab.	C_K (ml./min.)	P_{Osm} (mOsm./ L.)
13	C	7.02	498	11.64	4.62	4.88	13.981	.457	96.72	24	294
	D	5.85	468	9.16	3.31	5.19	9.010	.299	96.68	53	292
14	C	6.88	461	10.4	3.49	4.92	10.379	.551	94.67	19	293
	D	6.29	444	9.31	3.02	5.84	7.140	.308	95.68	39	285
15	C	9.21	372	11.58	2.37	4.09	8.346	.705	91.39		293
	D	6.69	356	8.22	1.53	3.59	5.947	.476	92.00		278
16	C	13.13	376	16.10	2.97	2.38	17.755	.683	96.25	12	295
	D	9.73	445	14.40	4.67	4.42	15.210	.630	95.86	22	286
17	C	12.4	459	20.2	6.70	4.40	21.930	1.038	95.04		298
	D	9.72	453	14.64	4.92	6.47	11.001	.699	93.97		295
18	C	6.62	422	9.08	2.46	2.81	12.822	.390	97.06	16	290
	D	5.30	569	9.80	4.40	6.19	10.368	.219	97.89	25	280

*V, urine flow. U_{Osm}, urine osmolality. C_{Osm}, osmolal clearance. Tc_{H2O}, free water reabsorption. L_{Na}, filtered sodium load. $U_{Na}V$, sodium excretion rate. %Na reab., per cent sodium reabsorption. C_K, potassium clearance. P_{Osm}, plasma osmolality.

osmolality diminished in the 6 patients in whom it was measured. Blood urea concentrations rose in 6 of 8 patients. Serum creatinine concentration was measured in 4 cases and did not change, in spite of depressed filtration rates. Arterial pressures, supine and standing, decreased in 6 of 8 patients.

Intravenous Injection

One hour after intravenous injection of 0.5 Gm. of chlorothiazide, renal plasma flow (C_{PAH}) was depressed in 2 and glomerular filtration in 1 of the 4 patients.

The largest renal change observed was a consistent decrease in sodium reabsorption, with increases in the rate of sodium excretion, potassium clearance, and absolute and relative rates of free water reabsorption.

DISCUSSION

The renal vascular bed is responsive to changes in blood volume, cardiac output, and sodium balance. Acute hypovolemia, such as results from moderate bleeding,[5] venous constion of the extremities,[6] and quiet standg,[7] decreases renal plasma flow, has little effect on filtration rate, and increases filtraon fraction. In contrast, during prolonged odium restriction with resultant chronic hypovolemia, such as results from the rice diet, renal plasma flow is well maintained, glomerular filtration rate falls, and filtration fraction diminishes.[8-10] The effects of prolonged administration of chlorothiazide on the renal vascular bed resemble those seen during low sodium dietotherapy. Since chlorothiazide causes depletion of sodium, water, and plasma volume, it would be premature to ascribe these changes in the renal circulation to sodium depletion as such. It may be that chronic hypovolemia leads to renal hemodynamic readjustments resulting in changes that have been attributed to sodium depletion alone.[9] Supporting this view is the fact that in the nephrotic syndrome—a condition characterized, in part, by chronic hypovolemia[11]—renal plasma flow may be unchanged or increased, filtration rate is usually depressed, and filtration fraction is consistently low. Against this interpretation is a study in 2 patients under treatment with the rice diet; in them infusion of salt-poor albumin did not increase filtration rate, while infusion of sodium lactate solution restored it to or towards control levels.[9]

Since chlorothiazide is excreted in part by proximal tubular secretion, apparently along a pathway similar to that of p-aminohippu-

TABLE 3.—*Effects of Intravenous Chlorothiazide on Renal Functions*

Patient no.	Study	C_{PAH} (ml./min./1.73 M.²)	$C_M \times 1.1$ (ml./min./1.73 M.²)	V	U_{Osm} (mOsm./L.)	C_{Osm} (ml./min./1.73 M.²)	T^cH_2O (ml./min./1.73 M.²)	C_K (ml./min.)	$U_{Na}V$ (mEq./min.)	% Na reab.
19	C	441	129	14.2	386	18.9	4.7	24	1.215	96.96
	D	324	95	13.1	430	19.1	6.0	48	1.427	87.09
20	C	683	119	10.0	483	16.0	6.0	32	.841	94.61
	D	601	111	10.7	491	17.3	6.6	93	1.006	92.61
21	C	356	55	5.0	421	6.7	1.7	21	.270	98.37
	D	376	62	9.2	411	11.6	2.4	23	.854	89.88
22	C	345	86	11.7	421	14.7	3.0	21	1.187	90.68
	D	393	85	15.2	432	20.4	5.2	44	1.763	84.44

rate,[12] it is not surprising that large intravenous doses depress renal extraction of p-aminohippurate in the dog. It is unlikely that this would account for the small decreases in plasma C_{PAH} in the tests done during oral administration, although it may account for the decreases observed in 2 patients after the intravenous injection.

The decreases in absolute rates of free water reabsorption observed during prolonged chlorothiazide administration obviously reflect depressed glomerular filtration. The increases in the relative rate of this function could be attributed to a dispersion of nephron function, such that glomerular filtration is largely in abeyance in some nephrons and persists in those nephrons whose longer tubules enhance their water reabsorptive function. However, both the absolute and relative rates of free water reabsorption increased after intravenous injection of the drug, without noteworthy changes in glomerular filtration. This suggests that the primary basis for the change in reabsorptive function, which implies an increase in renal "osmotic ceiling," may be increased osmolality of renal extracellular fluid in the regions of active water transport.[13]

Changes in sodium and potassium excretion after intravenous injection of the drug confirm earlier observations.[2] The changes in the prolonged experiments are of interest, in that decreased filtered sodium load usually stimulates sodium reabsorption. While this was observed in 1 patient of the prolonged series, the data indicate that chlorothiazide prevented increased sodium reabsorption in the others.

Changes in osmolality reflect the saluretic activity of the drug, and require no further comment. The increases of blood urea observed in some patients may be noteworthy, in that in some cases they seem to be greater than would be predicted from the concurrent decrease in filtration rate. One factor may be increased urea reabsorption, consequent on increased water reabsorption. However, this function was not measured. Another possibility is that chlorothiazide may indeed stimulate ammonia formation in the kidney, as may occur in hepatic cirrhosis, with the difference that this ammonia, in our subjects, could be converted to urea. This assumption implies a stimulation of glutaminase activity, but more evidence is required, both indirect from clearance studies and direct from studies of enzymatic activity.

SUMMARY

In addition to its recognized saluretic and kaluretic properties, prolonged oral administration of chlorothiazide to hypertensive patients often depresses glomerular filtration, causes an increase in blood urea that may be disproportionate, and, in the face of decreased filtered sodium load, tends to maintain a normal rate of sodium reabsorption. It also causes an increase in free water reabsorption which is evidenced only relatively in the prolonged experiments but which is also observed as an absolute increase, in tests done shortly after intravenous injection of the drug. Th

renal hemodynamic status during prolonged administration may be attributable to sodium depletion as such. However, by analogy with renal hemodynamic status in nephrosis, hypovolemia may be the primary factor.

Summario in Interlingua

A parte su recognoscite proprietates salu-retic e kaliuretic, le prolongate administration oral de chlorothiazido a patientes hyperten-sive deprime frequentemente le filtration glo-merular, causa un augmento del urea in le sanguine (a grados que pote devenir dispro-portionalmente alte), e—in le presentia de un reducite carga de natrium filtrate—tende a mantener un normal mesura in le reabsorp-tion de natrium. Illo etiam causa un augmen-to del reabsorption de aqua libere. Iste facto es evidente solmente de maniera relative in le experimentos prolongate, sed illo se observa etiam como un augmento absolute in tests effectuate brevemente post le injection intra-venose del droga. Le stato del hemodynamica renal durante cursos de administration pro-longate es forsan attribuibile al depletion de natrium per se. Tamen, per analogia con le stato del hemodynamica renal in nephrosis, il es possibile que hypovolemia es le factor primari.

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A Mechanism of Chlorothiazide-Enhanced Effectiveness of Antihypertensive Ganglioplegic Drugs

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Chlorothiazide decreases plasma volume, heart size, and cardiac output. The oligemia stimulates vasomotor tone; this tends to maintain arterial pressure because chronic arterial hypertension is characteristically self-sustaining and homeostatic. This oligemic stimulation of vasomotor tone results in increased sensitivity to the antihypertensive effect of drugs depressing or blocking vasomotor function.

A PRELIMINARY report,[1] on chlorothiazide-induced sensitization to the hypotensive effect of antihypertensive ganglioplegic drugs, described an association between the sensitization and reduction of plasma volume, and suggested that this depletion might be the primary mechanism. Other possible mechanisms were not excluded.

In the previous study we had anticipated that the depressor response to "bloodless phlebotomy" would be intensified during chlorothiazide treatment. Such an intensification was not found, and this seemed inconsistent with the concept of oligemia as the primary mechanism. However, Dr. James McCubbin, of this Division, suggested that the seeming paradox might be explained by increase in vasomotor activity that occurs during oligemia[2, 3] and, further, that increased vasomotor tone would also account for the enhanced responsiveness to ganglioplegic drugs such as occurs in the neurogenic hypertensive dog.[4]

This report describes experiments in which this concept was tested by indirect methods. The results are consistent with the concept.

METHODS

The effects of chlorothiazide on cardiac output, blood pressure, and total peripheral resistance were studied in 11 hospitalized hypertensive patients. The effects of "prolonged" administration were studied in 9 patients who received 1 Gm. of chlorothiazide* twice daily for periods ranging from 4 to 6 days, and effects of intravenous administration were studied in 2 patients who were given 500 mg. In the prolonged study, hemodynamic measurements were made before and at the end of the period of drug treatment, except in 3 patients in whom the sequence of observations was reversed. In the 2 patients who were studied after intravenous administration, measurements were made immediately before and 1 hour after the injection. One patient continued to take 200 mg. of hydralazine daily; the remaining patients received no vasoactive drugs during the period of chlorothiazide administration. To investigate further the enhanced responsiveness to ganglioplegic drugs induced by chlorothiazide, 7 patients were given tetraethylammonium chloride (TEAC) intravenously immediately after the control and "drug" observations had been made. Each patient received 5 mg./Kg. at a rate of 1 mg./Kg./min.; 5 and 15 minutes after the injection, cardiac output and blood pressure measurements were repeated. The effects of an infusion of 500 ml. of dextran were studied in 1 who was not given TEAC. Throughout the period of investigation blood pressure was measured 4 times daily in the supine and standing positions. In addition, heart size was determined in 12 patients from teleroentgenograms during both the control and "drug" periods. Six of these patients were from this study group. The remaining 6 were similarly treated during a study of chlorothiazide-induced changes in renal function.[5] Serum electrolytes were measured in most patients.

Cardiac output was determined in the supine position after a fast of at least 8 hours, by a dye-dilution technic with indigo carmine.[6] Dye was injected from a calibrated 5-ml. syringe into the antecubital vein and this was followed immediate-

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TABLE 1.—*Effects of Chlorothiazide on Cardiac Output and Related Functions**

tient no.	Study	C.I. (L./min./M.²)	MBP (mm. Hg)	TPR dynes/ sec./cm.⁻⁵	CBV (ml.)	PV (ml.)	Body weight (lbs.)	Blood pressure average (mm. Hg) Supine	Standing
1	C	3.6	132	1694	2664	2513	155	160/107	142/107
	D	3.2	107	1531	2496	2235	153	136/98	120/89
2	C	3.1	111	1554	2787		158	159/92	150/95
	D	2.3	106	1936	2347		155	143/92	130/89
3	C	2.2	170	3327	2203	2680	161	217/128	205/130
	D	1.8	171	4091	1767	2514	157	220/128	198/124
4	C	3.6	120	1670	2219	1875	122	185/110	159/102
	D	2.9	116	2072	1657	1481	118	150/100	125/93
5	C	3.3	141	2023	2664		157	189/108	168/108
	D	1.9	125	3166	1482		147	157/100	134/96
6	C	3.2	138	2105	2509	2460	137	186/118	181/119
	D	2.7	140	2506	2081	2120	133	169/109	162/110
7	C	3.8	130	1450	3262	2827	177	176/113	167/107
	D	3.1	119	1599	2796	2409	173	140/85	128/83
8	C	3.3	153	2037	2908	2888	168	177/114	145/108
	D	2.3	130	2506	2389	2504	164	153/104	130/99
9	C	2.6	160	2780	2416	3020	163	243/135	235/132
	D	2.0	159	3605	1788	2460	160	235/127	213/127
Means	C	3.2	139	2072	2626	2609	155	188/114	172/112
	D	2.5	130	2557	2089	2246	151	167/105	149/101
Percentile changes		—23	—6	+23	—21	—14	—3	—11/—8	—13/—10

*C.I., cardiac index. MBP, mean blood pressure. TPR, total peripheral resistance. CBV, central blood volume. C, control observations. D, chlorothiazide observations. PV, plasma volume.

by an injection of 8 ml. of saline. The curve of dye concentration was obtained by drawing brachial arterial blood through a cuvet densitometer[7] by means of a constant flow system.[8] The curve was calibrated by timed collection of a pooled sample.[8] Dye concentration of the plasma of the pooled sample was measured in a Coleman 6A spectrophotometer at 600 mμ. Intraarterial pressure was measured with a strain gage and a Sanborn direct-writing recorder. Mean blood pressure (MBP) was obtained from the recording by planimetry. Mean circulation time (MCT) was calculated from the formula MCT = C × t/C, and central blood volume (CBV) from the formula CBV = MCT × CO (cardiac output). In 6 patients the control studies were carried out before chlorothiazide was given, while in the remaining the sequence was reversed and control values were obtained after discontinuance of the drug.

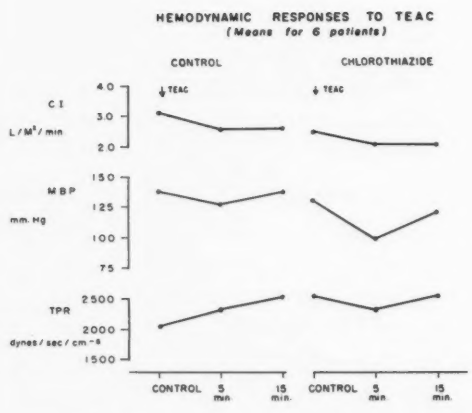
Plasma volume was estimated from the volume of distribution of radio-iodinated serum albumin.[9]

[7] Colson Corporation, Elyria, Ohio.

RESULTS

Changes Induced by Prolonged Administration of Chlorothiazide

Cardiac Output and Related Functions. The effects of the prolonged administration of chlorothiazide on cardiac output and related functions were studied in 9 patients (table 1). In 7 cases control values for cardiac index (cardiac output in L./min./M.²) represent averages of 2 determinations (within 10 minutes). The variations between means of the 2 measurements averaged 4.7 per cent. Control values were within normal limits,[10] averaging 3.2 L./min./M.² In all patients output diminished after several days of chlorothiazide administration. The decreases ranged from 11 to 42 per cent (mean 23). Mean arterial pressure (MBP), calculated



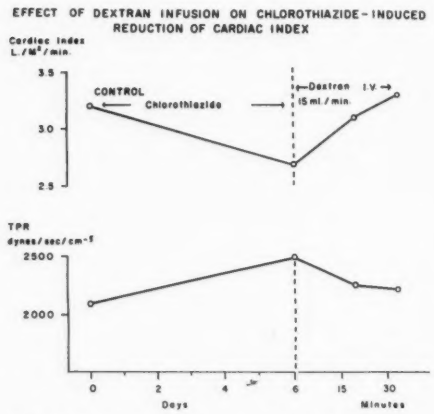


FIG. 1 *Left.* Means of observations of the effects of TEAC on cardiac output (stated here as *CI*), mean blood pressure, and total peripheral resistance before and after administration of chlorothiazide, with enhanced depressor response after chlorothiazide and a decreased rather than an increased total peripheral resistance.

FIG. 2 *Right.* Decrease in cardiac output and increase in total peripheral resistance as the result of 6 days' treatment with chlorothiazide and return of these functions to control levels over the course of 30 minutes' infusion of dextran. Pretreatment mean blood pressure 138 mm. Hg, after chlorothiazide 140 mm. Hg, at the end of dextran infusion 150 mm. Hg.

from measurements made at the time of the output determination, was lower in 6 of the 9 patients after chlorothiazide, and was unchanged in 3. The calculated total peripheral resistance during the control study averaged 2,072 dynes/sec./cm.$^{-5}$, and at the end of the experimental period was increased in 8 by a mean of 27 and decreased in 1 by 10 per cent. Central blood volume decreased by a mean of 21 per cent. Mean circulation time was prolonged in 4 of the 9 patients.

Plasma Volume. This measurement was made in 7 patients, and consistent decreases averaging 14 per cent were observed after chlorothiazide.

Responses to TEAC. In 6 of the 7 patients tetraethylammonium chloride (TEAC) had consistent effects (fig. 1). In both test situations (without or during chlorothiazide) TEAC injections were followed by decreases in cardiac output (CI) which averaged 16 per cent less than the pre-injection values. Blood pressure changes were transient during the control study; mean blood pressure was decreased by a mean of 11 mm. Hg at 5 minutes after injection, and returned to pre-injection levels at 15 minutes. Chlorothiazide treatment intensified the blood pressure response to TEAC; at 5 minutes mean blood pressure decreased by a mean of 31 mm. Hg and did not return to the pre-injection values in 15 minutes. Total peripheral resistance during the control study rose after TEAC injections. During chlorothiazide treatment total peripheral resistance was elevated and TEAC then caused a slight fall at 5 minutes, but by 15 minutes the values returned to pre-injection levels. In the 1 patient TEAC increased cardiac output and decreased arterial pressure both with and without chlorothiazide.

Infusion of Dextran. To explore the possibility that decreases in cardiac output during chlorothiazide administration were due to hypovolemia, 1 patient, who had been given chlorothiazide for 6 days and had sustained a 16 per cent decrease in cardiac output, was given 500 ml. of dextran intravenously (fig. 2). This infusion was started immediately after the determination of cardiac output; it was given at a rate of 15 ml./min.; output measurements were repeated after 300 ml. and 500 ml. of dextran had been given. The initial infusion of dextran increased blood pressure and cardiac output and decreased

tal peripheral resistance; at the time of ie second measurement, cardiac output was stored to, and blood pressure was greater ian, the pre-treatment level.

Other Observations. Serum electrolytes ere measured before and during chlorothiazide administration. Serum sodium fell an verage of 6 mEq./L., potassium 0.6 mEq./L., loride 4 mEq./L., while CO_2 content increased by 3.8 mEq./L. All patients lost eight; these losses averaged 3.0 per cent ody weight. The averages of blood pressures aken 4 times daily, lying and standing, were ss during the administration of the diuretic in 7 patients (table 1). Supine blood pressure showed a mean decrease of 23/9 mm. Hg and standing blood pressure decreased 23/11 mm. Hg. The transverse cardiac diameter was less in all patients during chlorothiazide administration regardless of the original heart size (table 2). The decreases in transverse cardiac diameter ranged from 0.8 to 2.5 cm. and the average was 1.3 cm. Three patients were studied again after chlorothiazide had been withdrawn, and, in each, heart size was found to have returned to the control value.

TABLE 2.—*Changes in Transverse Cardiac Diameter (TCD) Evoked by Chlorothiazide**

Patient no.	TCD (cm.) C	D	Patient no.	TCD (cm.) C	D
2	16.5	14.5	10	16.0	15.0
4	12.4	11.6	11	16.4	16.5
5	14.5	13.0	12	16.3	13.8
6	13.0	12.0	14	11.5	10.0
7	15.3	14.5	17	13.0	11.4
9	16.5	14.5	18	14.3	12.2

*See footnote, table 1.

Effects of Intravenous Chlorothiazide

Cardiac output, mean blood pressure, and total peripheral resistance were not affected in 2 patients 1 hour after they had received 500 mg. of chlorothiazide intravenously (table 3).

Discussion

Cardiac Output and Related Functions. The concurrence of decreased plasma volume, heart size, large decreases in cardiac output, small decreases in arterial pressure, increases of total peripheral resistance, and increased sensitivity to the depressor effect of TEAC is consistent with the view that the primary factor in determining chlorothiazide enhancement of the effects of ganglioplegic antihypertensive drugs is contraction of plasma volume, partially compensated for by increased motor tone.

The fact that TEAC had not more depressant effect on cardiac output during than it had without chlorothiazide might seem inconsistent. It is reasonable to suppose, however, that the arterial vasodilator effect of TEAC would be enhanced in the presence of increased vasomotor tone, and this assumption is supported by the fact that TEAC decreased total peripheral resistance during chlorothiazide treatment, whereas without treatment the reverse was the case. This enhanced vasodilator activity on the arterial side is apparently sufficient to offset the depressant effect on cardiac output of the venomotor paresis elicited by this ganglioplegic agent.

The observations are therefore consistent with the hypothesis that oligemia with increased vasomotor activity is the primary mechanism by which chlorothiazide potentiates the action of drugs that, like reserpine, depress, or, like the antihypertensive ganglioplegics, interfere peripherally with vasomotor outflow. This action results in a therapeutic advantage which we[1] and others[11] have described.

Sodium Loss as a Possible Primary Mechanism. Chlorothiazide causes a depletion of both sodium and water, and these effects are not easily separated. Sodium depletion might be antihypertensive by its effect on blood volume or, hypothetically, by withdrawing salt and water from the walls of arteries and arterioles. That the effect of chlorothiazide depends primarily on volume rather than on some action of the sodium ion is suggested by the one observation in which salt-free dextran restored cardiac output and arterial pressure during chlorothiazide-induced oligemia. As concerns the possible effects of "dehydration" of vessel walls, it should be noted that, with the exception of one patient, total peripheral resistance increased and did not decrease during treatment with chlorothiazide.

TABLE 3.—*Effects of Intravenous Chlorothiazide on Cardiac Output and Blood Pressure**

Patient no.	Study	C.I. (L./min./M.²)	MBP (mm. Hg)
19	C	2.9	140
	D	2.9	137
20	C	3.3	121
	D	3.3	121

*See footnote, table 1.

Effects of Intravenous Chlorothiazide. The fact that intravenous injection of chlorothiazide has no effects on arterial pressure, cardiac output, and peripheral resistance over the course of 1 hour demonstrates that chlorothiazide as such has no direct vasotropic hypotensive action.

Depressor Effect of Chlorothiazide Given Alone. A minority of patients respond by large decreases in arterial pressure to chlorothiazide alone, in the absence of other antihypertensive drugs.[11] Presumably this depends on the same mechanism that determines responsiveness to strict low-sodium dietotherapy.[12, 13] The basic mechanism may be loss of body sodium as such or an unusual susceptibility to small decreases in blood volume. Decreased blood volume has also been observed during treatment with the rice diet.[13, 14] This implies that chlorothiazide can be used as a means of selecting and quantitating some of the various mechanisms of essential hypertension.

Homeostasis of Hypertension. We conceive of essential hypertension as a state resulting from the interplay of different etiologic factors whose equilibrium has been displaced in the direction of increased arterial pressure.[15] Once established, the process tends to be self-sustaining, and the relief or removal of the primary factor may or may not relieve the hypertension, depending in part on the duration of the process. Clinical impressions with drug therapy and experience with nephrectomy in renal hypertension exemplify this generalization. A specific example was the experience in treatment of hypertension with phenoxybenzamine,[16] an anti-adrenergic agent that blocks or damps the vasomotor component in hypertension. In some patients notably those selected as probably having "neurogenic"[17] hypertension, this agent caused a prompt decrease in supine blood pressure. Over the course of several days however, supine blood pressure rose to pre treatment levels, in spite of increasing dosage continued adrenergic blockade, and defective vasomotor function manifested by orthostatic hypotension. This sequence demonstrates the relief of one component in hypertension which may have been primary, and its replacement by some other pressor mechanism.

This process is also exemplified in the dog with renal hypertension, in which, with the course of time, the buffer nerves "re-set" so that this system ultimately tends to maintain, by a neurogenic mechanism, a hypertension that was primarily renal.[18] The action of chlorothiazide in hypertension is still another case in point. Here, however, therapeutic advantage is taken of this interesting natural phenomenon. The sequence, in most patients, is that chlorothiazide decreases plasma volume and thus tends to decrease arterial pressure. The "homeostasis" of hypertension then results in increased vasomotor tone, tending to sustain pressure. At this point the administration of an agent which diminishes vasomotor tone reduces arterial pressure more effectively than it would in the absence of increased vasomotor tone.

SUMMARY AND CONCLUSIONS

Chlorothiazide, orally administered to hypertensive patients over the course of a few days, decreases plasma volume, heart size, cardiac output, and increases total peripheral resistance in most, and also sensitivity to the depressor effect of intravenously injected TEAC, without affecting the depressant effect of TEAC on cardiac output.

The data are consistent with the view that the primary mechanism by which chlorothiazide enhances responsiveness to the antihypertensive effects of drugs acting on the vasomotor system is that it causes oligemia which evokes intensification of vasomotor tone. This increases the fraction of the hypertensi

which is sustained by the vasomotor system, establishing a degree of neurogenic hypertension, which is susceptible to relief by such drugs.

Summario in Interlingua

Chlorothiazido, quando administrate per via oral a patientes hypertensive durante un curso de plure dies, reduce le volumine del plasma, le dimensiones del corde, e le rendimento cardiac e augmenta—in le majoritate del casos—le total resistentia peripheric e le sensibilitate al effecto depressori de chloruro de tetraethylammonium, sed illo non affice le effecto depressori de chloruro de tetraethylammonium super le rendimento cardiac.

Iste datos es compatibile con le concepto que le mechanismo primari per que chlorothiazido promove le responsivitate al potential antihypertensive de drogas que age super le systema vasomotori consiste in le facto que illo causa oligemia le qual, de su parte, evoca un intensification del tono vasomotori. Isto augmenta le parte del hypertension que es sustenite per le systema vasomotori e establi un grado de hypertension neurogene que es susceptibile de esser alleviate per tal drogas.

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Depressive Reactions in Hypertensive Patients

A Comparison of Those Treated with Rauwolfia and Those Receiving No Specific Antihypertensive Treatment

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Because of reports that derivatives of Rauwolfia serpentina may cause severe mental depression when used in the treatment of hypertension, the depressive reactions and possible contributing factors were studied in a group of 387 hypertensive patients. Some of the patients received no specific antihypertensive medication; some were treated with Rauwolfia derivatives alone and some with Rauwolfia and other antihypertensive drugs. Of the patients receiving Rauwolfia, alone or with other drugs, 26 per cent experienced depressive reactions whereas only 5 per cent of the others had them.

SINCE 1954 reports have indicated that derivatives of Rauwolfia serpentina may cause serious mental depression when used in the treatment of patients with arterial hypertension. Freis[1] reported mental depression in 5 hypertensive patients following several months of treatment with reserpine in doses as low as 0.25 mg. a day. Wallace,[2] in a study of several different antihypertensive programs, noted depression in 4 of 44 patients taking reserpine with or without pentolinium, and in only one of 88 patients treated without Rauwolfia. Additional reports[3-10] in succeeding years have furnished more examples of depression occurring among hypertensive patients treated with Rauwolfia, and therefore have added weight to the suggestion that caution is needed in the use of these preparations.

Usually it has been stated that depressive reactions occur more frequently among hypertensive persons treated with Rauwolfia who had experienced some previous psychologic difficulty. However, it is not clear from these reports whether previous psychiatric problems are more frequent in those patients who become depressed as contrasted with those who do not. Wallace[2] and Lemieux and associates[3] compared the frequency of depressive reactions among their hypertensive patients treated with Rauwolfia with the infrequency of such reactions in patients treated with other antihypertensive drugs. We are not aware of any reports on the frequency with which depression may be expected among hypertensive patients not taking such medicaments. Also, the two reports cited do not make it clear whether the patients treated with Rauwolfia compounds were closely comparable as a group to the other patients studied, nor whether any particular features distinguish those who suffered a depressive reaction from those who did not.

The present study was undertaken to determine whether there are any factors that may contribute to the occurrence of depression in hypertensive patients, whether Rauwolfia drugs actually do enhance the production of such reactions, and whether it is possible to predict which patients may be especially susceptible to a depressive reaction.

Methods

Records were reviewed of all residents of Rochester, Minnesota, who were seen at the Mayo Clinic during the 2 years from January 1, 1954, through December 31, 1955, for whom a diagnosis of hypertension was recorded. Of 863 patients given this diagnosis, 391 were selected for further study because there was good evidence that their blood pressure levels were well sustained at values

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TABLE 1.—*Basic Data Regarding Patients Studied*

	No specific antihypertensive medication	Rauwolfia	
		Alone	Combined with other treatment
Number of patients	185	154	48
Average age (yrs.)	66	61	58
Sex			
Male	40 (22%)	37 (24%)	15 (31%)
Female	145 (78%)	117 (76%)	33 (69%)
Avg. known duration of hypertension (yrs.)	11	11	12
Average blood pressure (mm. Hg)			
Before treatment	198/109	201/112	213/121
During treatment	195/107	176/99	185/105
Past history of depression	7 (4%)	16 (10%)	3 (6%)
Arteriolar changes in ocular fundi*			
Group 1-2	75 (41%)	100 (65%)	30 (63%)
Group 3-4	7 (4%)	8 (5%)	9 (19%)
Complicating disease			
Cardiac	94 (51%)	85 (55%)	26 (54%)
Cerebral	38 (21%)	45 (29%)	8 (17%)
Renal	17 (9%)	19 (12%)	3 (6%)
None	79 (43%)	53 (34%)	18 (38%)

*Grouping according to Keith-Wagener-Barker classification. Data not available for some patients.

of 175 mm. Hg systolic and 100 mm. diastolic, or higher. The remainder did not have sustained blood pressure of this magnitude, and were not included in the study.

The 391 patients were divided into groups on the basis of treatment that had been given for the hypertension. The first group received no specific antihypertensive medication. For the purpose of this study, sedatives, including barbiturates, were not considered to be specific antihypertensive medicaments. The second group received no specific antihypertensive medication other than some form of Rauwolfia serpentina. The third group was given some form of Rauwolfia medication and, for at least part of the period studied, some additional antihypertensive drug. Four persons received specific antihypertensive drugs exclusive of Rauwolfia. This number was too small for comparative purposes, and consequently data on this group are not included in this report. The details presented, then, concern 387 patients. Although some patients in the 3 groups received other forms of medication for a variety of co-existing conditions, these drugs were not considered in the present study.

Within the 3 groups studied, the patients were classified as to whether they had shown no evidence of depression, or evidence of mild, moderately severe, or severe depression. Mild depression was arbitrarily defined as a subjectively sad or depressed feeling noted by the patient, or a reaction which the clinician described as "depression" without additional amplifying information. For example, it was not uncommon to find a note, without any clue as to the specific symptoms, that merely stated, "Has been a little depressed the past two weeks; discontinue reserpine." Such cases were classified as mild depression. Moderately severe depression was defined as any depressive reaction characterized by the addition of one or more of the following symptoms: anorexia, loss of weight, frequent crying spells, early morning awakening, preoccupation with death, psychomotor retardation or agitation not requiring hospital treatment, and suicidal thoughts or desires not accompanied by any real intent of committing suicide. We also classified as moderately severe any depression which led the physician to advise psychiatric consultation. Severe depression was defined as any depression requiring hospitalization or resulting in an attempt to commit suicide.

In addition certain basic factors were studied (table 1).

Although reserpine, deserpidine, and Rauwolfia alkaloids other than reserpine are reported to have appreciable hypotensive activity, there is good evidence that the major active principle in the whole root and alseroxylon preparations of

TABLE 2.—*Patients Depressed During Two-Year Period of Study*

	No specific treatment (185 patients)		Rauwolfia			
			Alone (154 patients)		Combined with other treatment (48 patients)	
	No.	Per cent	No.	Per cent	No.	Per cent
Mild depression	3	2	28	18	4	8
Moderately severe depression	3	2	8	5	5	10
Severe depression	3	2	7	5	1	2
All types of depressions	9	5	43	28	10	21

Rauwolfia serpentina is reserpine.[4, 11–17] Therefore, in order to facilitate analysis of results, we converted all drug forms to an equivalent dose of reserpine on the basis of 1,000 units of whole root extract or 10 units of the alseroxylon fraction as representing the equivalent of 1 unit of reserpine.* Therefore, unless otherwise specifically stated, the term Rauwolfia is used to include all of these preparations, and the dosage is expressed as the equivalent dose of reserpine.

RESULTS

Information on the basic factors concerning the patients selected for study is summarized in table 1.

Depressive Reactions among Patients Receiving No Specific Antihypertensive Medication. This group consisted of 185 patients, of whom 9 (5 per cent) experienced some depressive reaction (table 2). All of the depressed patients were women; three of the reactions were mild, three moderately severe, and three severe.

The patients in this group were somewhat older than those in the treated groups and this may have been one reason why they were not treated more vigorously. The pretreatment blood pressure and the frequency of severe changes in the ocular fundi in this group of patients were comparable to those treated with Rauwolfia alone, but less severe than in the group treated with a combination of Rauwolfia and other antihypertensive drugs. Many of the patients in this "untreated" group were seen only sporadically, so that it was not possible to correlate the occurrence of depressions with changes in blood pressure.

Depressive Reactions among Patients Receiving Rauwolfia Only. The patients in this group were of about the same average age as those treated with a combination of drugs, but they had a lower average blood pressure and fewer had severe changes in the ocular fundi. This "Rauwolfia alone" group consisted of 154 patients, 43 (28 per cent) of whom became depressed (table 2). In 28 the depressive reactions were mild, in 8 moderately severe, and in 7 severe. Depressive reactions occurred in substantial numbers regardless of which preparation of Rauwolfia was used: 5 depressions were noted among 9 patients who were given only the whole root extract; 6 reactions among 31 persons who received solely the alseroxylon fraction; 21 depressions among 70 patients treated only with reserpine; and 11 of 44 persons who received more than one of these preparations during the period studied also showed some mental depression. Similar results have been reported previously in regard to whole root and reserpine.[4, 5]

Depressive Reactions among Patients Receiving Rauwolfia Combined with Other Antihypertensive Therapy. Rauwolfia preparations and in addition one or more other antihypertensive drugs were given to all patients in this group: veratrum preparations to 29; potassium thiocyanate to 6; ganglion-blocking agents to 21, and hydralazine to 12. The average duration of treatment with these additional preparations was 11 months and infrequently coincided exactly with the use of Rauwolfia. The average pretreatment blood pressure in patients in this group was higher and arteriolar changes in the fundi were more severe in more patients than in the other

*Some reports suggest that 20 mg. of alseroxylon fraction may be more nearly equivalent to 1 mg. of reserpine.[18]

groups, but the differences are not great table 1).

The total number of patients in this "combined treatment" group was 48, of whom) (21 per cent) experienced depressive re- tions. These were mild in 4, moderately vere in 5 and severe in 1 patient. The rugs taken in combination with Rauwolfia by ese 10 depressed patients included pento- nium taken by 8, potassium thiocyanate by veratrum preparations by 5, and hydrala- ne by 3. Except for Rauwolfia, no one drug combination of drugs occurred sufficiently ten to permit the conclusion that they had any tendency to enhance depression.

Combined Group. This grouping includes all patients who received Rauwolfia, whether alone or as part of combined therapy. Of the total of 202 patients, 53 (26 per cent) experienced a depressive reaction. This was mild in 32 (16 per cent), moderately severe in 13 (6 per cent), and severe in 8 (4 per cent) of the patients.

The Relation of Depression to Reduction of Blood Pressure. The nature of this study made it difficult to compare pretreatment and post-treatment blood pressure in some patients, because in many instances determinations were made infrequently and not under well standardized conditions. The blood pressures therefore do not have the same validity as those derived from more closely controlled studies. Realizing these limitations, we attempted to determine whether any obvious correlation existed between depressive reactions and the degree of reduction of the blood pressure as a result of treatment. The results are shown in tables 3 and 4. There is a suggestion that the severely depressed patients had a greater average lowering of diastolic blood pressure than those who did not become depressed, but this is largely due to a great drop in both systolic and diastolic pressures on the part of 1 patient. We do not consider that there is any substantial relationship between the degree of lowering of the blood pressure and the occurrence of depressions, either in the treated or in the untreated group.

TABLE 3.—*Combined Group of 202 Patients Receiving Rauwolfia: Comparison of Depressed and Nondepressed Patients*

	No depression	Depression
Number of patients	149	53
Average age (yrs.)	60	61
Sex		
Male	39 (26%)	13 (25%)
Female	110 (74%)	40 (75%)
Average known duration of hypertension (yrs.)	11	11
Average blood pressure (mm. Hg)		
Before treatment	190/115	203/114
During treatment	178/99	181/101
Past history of depression	8 (5%)	11 (21%)
Arteriolar changes in ocular fundi*		
Group 1-2	96 (64%)	34 (64%)
Group 3-4	13 (9%)	4 (8%)
Complicating disease		
Cardiac	83 (56%)	27 (51%)
Renal	17 (11%)	5 (9%)
Cerebral	40 (27%)	13 (25%)

*Grouping according to Keith-Wagener-Barker classification. Data not available for some patients.

Funduscopic Groupings. Severe (groups 3 and 4) hypertensive changes in the ocular fundi were reported in 4 (8 per cent) of the 53 patients who experienced depression while taking Rauwolfia and in 13 (9 per cent) of the 149 patients who did not become depressed. The frequency of various degrees of hypertensive changes in the ocular fundi for each degree of severity of depression among Rauwolfia-treated patients is shown in table 4. The severity of hypertension, as judged by this particular index, does not appear to have an appreciable effect on the occurrence of depression among patients treated with Rauwolfia. Among the untreated patients, severe changes in the ocular fundi were so infrequent that no conclusions were possible.

Cardiac Complications. Cardiac abnormalities, varying from severe congestive failure and myocardial infarctions to minimal electrocardiographic evidence of left ventricular

TABLE 4.—*Relation of Hypertension and Complications to Severity of Depression in 202 Patients Receiving Rauwolfia*

	Severity of depression		
	Mild	Moderately severe	Severe
Number of patients	32 (16%)*	13 (6%)*	8 (4%)*
Average age (yrs.)	63	57	60
Sex			
Male	9 (28%)†	1 (8%)†	3 (38%)†
Female	23 (72%)	12 (92%)	5 (62%)
Average known duration of hypertension (yrs.)	10	12	12
Average blood pressure (mm. Hg)			
Before treatment	204/112	200/116	208/115
During treatment	187/103	169/102	179/93
Past history of depression	5 (16%)	6 (46%)	0
Arteriolar changes in ocular fundi‡			
Group 1-2	19 (59%)	11 (85%)	4 (50%)
Group 3-4	1 (3%)	1 (8%)	2 (25%)
Complicating disease			
Cardiac	21 (66%)	4 (31%)	2 (25%)
Renal	3 (9%)	2 (15%)	0
Cerebral	9 (28%)	1 (8%)	3 (38%)

*Per cent of 202 patients in combined groups receiving Rauwolfia.

†Per cent of patients having depression of same degree.

‡Grouping according to Keith-Wagener-Barker classification. Data not available for some patients.

hypertrophy, were present in 110 of the 202 patients who received Rauwolfia. The distribution of these complications among the depressed and nondepressed patients is shown in tables 3 and 4. The presence or absence of cardiac disease did not appear to be a factor influencing the development of a depressive reaction.

Cerebral Complications. A history of hypertensive crises, definite cerebral infarction, or clinical evidence of cerebral arterial insufficiency was classified as a cerebral complication. Such findings were present in 13 (25 per cent) of those patients who became depressed while taking Rauwolfia and in 40 (27 per cent) of those who did not become depressed while taking such drugs (tables 3 and 4). Among those patients who were not given Rauwolfia, similar complications existed in 4 (44 per cent) of those who became depressed and in 34 (19 per cent) of those who did not experience depression. Thus it seems that there was no distinct relationship between cerebral vascular disease and mental depression among the Rauwolfia-treated patients. On the other hand, such disease may have been an influencing factor in some of the depressive reactions that developed among the group of patients not receiving Rauwolfia.

Renal Complications. Disturbance in renal function of varying degree was noted clinically in 17 (9 per cent) of the 185 patients who did not receive Rauwolfia, but none occurred among the 9 patients in this group who became depressed. The occurrence of renal disease in patients who took Rauwolfia is shown in tables 3 and 4. Our study revealed no apparent relationship between renal complications and depressive reactions.

Age. The average age of patients who became depressed while taking Rauwolfia was about 1 year more than that of patients who did not experience a depression, with the range of age extending from 46 to 80 for men and 36 to 78 for women (table 5). There

ore age appeared to be of no importance in ttempting to determine which patients were ıost vulnerable to a depression. However, mong those patients not taking Rauwolfia the lepressions did seem to occur chiefly in the lder patients.

Sex (Table 6). In the untreated group none f the men, as opposed to 6 per cent of the omen, became depressed, while in the groups reated with Rauwolfia, depressive reactions leveloped about as frequently in men as in he women.

History of Depression. Of the 202 patients who received Rauwolfia 19 had a history of ıental depression prior to the use of Rauwolfia and 11 (58 per cent) of these 19 exhibited a depressive reaction during treatment. In 4 of these the history of a previous depression was obtained only after they became depressed while using Rauwolfia. Five patients still had a suggestion of depression at the time they started taking Rauwolfia, and 4 (80 per cent) of these 5 became more depressed while taking the drug. Of the other 14, 7 (50 per cent) became depressed. If all 19 of the patients with a past history of depression are omitted from the consideration, this would reduce the number of those who became depressed to 42 (23 per cent of the remaining 183 patients treated with Rauwolfia). Among the 42 are all of the 8 patients who had the most severe depressive reactions. Thus the absence of a history of depression did not lower remarkably the incidence of depressive reactions during the use of Rauwolfia.

Because of the type of material being anaıyzed, no attempt was made to correlate the ıcidence of depression with personality probems other than with a clear-cut history of epression.

These data justify 2 important conclusions: 1) that persons with a prior history of deressive reactions are likely to have such rections while taking Rauwolfia, and (2) that substantial number of persons who have o apparent past or present history of deression may still experience severe depresion while under treatment with Rauwolfia.

TABLE 5.—*Correlation of Average Age in Years and Depression*

	No specific antihypertensive medication (185 patients)	All patients receiving Rauwolfia (202 patients)	All groups (387 patients)
No depression	65.6	60.3	63.2
Depression, all patients	70.2	61.2	62.5
Mild	68.7	63.3	63.7
Moderately severe	81.3	57.1	61.6
Severe	60.7	59.5	59.8

Dose of Rauwolfia. The average daily dose of Rauwolfia, expressed as milligrams of reserpine, was 0.53 mg. for those patients receiving only Rauwolfia, 0.65 mg. for those on combined treatment, and 0.55 mg. for the entire number of patients who received Rauwolfia (table 7). The average dose given to the patients who became severely depressed was a little higher (0.62 mg.). However, many patients took much larger doses for many months without becoming depressed, and no patient in this study became depressed while taking less than 0.2 mg. a day.

Although there is great individual variation in tolerance of Rauwolfia, for long-term treatment the dose should be not more than 0.25 to 0.5 mg. a day. This is in accord with the recommendations of many others but is lower than that recommended by Lemieux and associates.[3]

Duration of Treatment with Rauwolfia. The duration of treatment with Rauwolfia varied from a few days to 24 months, the average being 8 months for those patients who experienced depression and 10 months for those who did not. The onset of depression was often insidious, and Rauwolfia was not always discontinued at the time of the first symptoms. The average duration of treatment with Rauwolfia before the onset of depressive symptoms was only 5 months. Thirty-two (60 per cent) of the depressions occurred within the first 6 months of treatment, 15 (28 per cent) during the interval from 6 to

TABLE 6.—*Relation of Sex to Occurrence of Depressive Reaction*

	No specific antihypertensive medication	Rauwolfia		
		Alone	Combined with other treatment	Entire group
Males	40	37	15	52
Depression	0	10 (27%)	3 (20%)	13 (25%)
Mild	0	8 (22%)	1 (7%)	9 (17%)
Moderately severe	0	0	1 (7%)	1 (2%)
Severe	0	2 (5%)	1 (7%)	3 (6%)
No depression	40 (100%)	27 (73%)	12 (80%)	39 (75%)
Females	145	117	33	150
Depression	9 (6%)	33 (28%)	7 (21%)	40 (27%)
Mild	3 (2%)	20 (17%)	3 (9%)	23 (15%)
Moderately severe	3 (2%)	8 (7%)	4 (12%)	12 (8%)
Severe	3 (2%)	5 (4%)	0	5 (3%)
No depression	136 (94%)	84 (72%)	26 (79%)	110 (73%)

12 months, and only 6 (11 per cent) came on after 1 year.

More important than the average duration of treatment, however, is the great variation encountered. One patient became depressed in less than 1 month on a dose of 0.5 mg. a day. Another individual took 2.0 mg. daily for 20 months during the period studied without becoming depressed, only to become depressed 6 months later while taking the same dose. Although it appears that most depressive reactions will be manifest within the first 6 months of treatment, no patient taking Rauwolfia should ever be considered safe from the risk of depression, no matter how long he may have tolerated the drug. The physician, the patient, and the patient's family should continue to be constantly alert for signs of depression in any person receiving Rauwolfia.

Symptomatology. The gross clinical features of the depressions that occurred in patients taking Rauwolfia were not particularly distinctive. Sometimes symptoms cleared up while patients continued to take substantial doses of the same Rauwolfia preparation. Most of the mild and some of the moderately severe depressions cleared promptly, after treatment with Rauwolfia was discontinued. Many of the moderately severe depressions, however, required additional medical therapy as well as some form of psychotherapy. The depressions cleared gradually in most cases, so that it was not possible to determine the average length of time that a depressive reaction lasted following cessation of the use of Rauwolfia.

Of the 8 patients with severe depression, some displayed chiefly agitation while others were retarded; 1 person made homicidal threats and there were 2 attempts at suicide, 1 of which was successfully carried out. Five of these 8 patients required electroconvulsive therapy to treat the depression adequately.

Nightmares were mentioned by many patients, and these were usually unpleasant, although 1 patient even enjoyed her exciting dreams. Many patients who otherwise tolerated the drug well had nightmares, and these seemed to have no relationship to depressive reactions.

COMMENT

It was not surprising that mental depressions were found more frequently among patients treated with preparations of Rauwolfia serpentina than among those who did not receive this drug. However, it was disconcerting to find that depressive reactions were 5 times more frequent in the Rauwolfia group and occurred in 26 per cent of all patients who received this drug. The implications of these observations are sufficiently important to warrant further consideration regarding their validity.

By using a level of blood pressure that was definitely hypertensive and by including only local residents who could return for observation as needed, it seems to us that the persons selected compose groups that are comparable in most respects. Although the "untreated" hypertensive patients were somewhat older than those given Rauwolfia preparations, the two groups do not differ significantly with respect to number of patients, sex distribution, known duration of hypertension, degree of hypertension, or associated complicating disease. In addition, the same group of physicians treated all of the patients concurrently under similar circumstances, so that variations in approach to the patient were probably not a major consideration. Thus the group of patients who received no specific antihypertensive treatment and the groups of patients receiving Rauwolfia were closely comparable.

A factor that might have increased the number of depressions among patients treated with Rauwolfia is the possibility that this group was subjected to closer scrutiny for evidence of depression than those persons who received no specific treatment. As a result of such observation more mild depressions may have been recorded among the Rauwolfia-treated patients. However, this possibility seems unlikely for 2 reasons. 1. This study covered a 2-year period when the various preparations of Rauwolfia serpentina had been introduced into general use only rather recently. At that time there was little general knowledge that these medicaments frequently were associated with serious mental depression. Consequently, it is unlikely that many patients did not receive Rauwolfia because their physicians feared this complication. By the same token the physicians would not be particularly alerted for evidence of depression among patients receiving Rauwolfia. 2. The significance of mild depressions is debatable, and the frequency of their occurrence is variable. For this reason the depressive reactions were graded as mild, moderately severe, and severe. By eliminating the mild group we still found a 3-fold increase in the moderately severe and severe depressive reactions among patients treated with Rauwolfia, and it is unlikely that such depressions would be overlooked or deemed unimportant in any patient. Under these circumstances the propensity of Rauwolfia for producing depression is still clearly evident.

TABLE 7.—*Relation of Dose* of Rauwolfia to Depressive Reactions*

	Rauwolfia		
	Alone	Combined with other treatment	Entire group
No depression	0.52	0.68	0.56
Depression	0.53	0.65	0.55
Mild	0.56	0.56	0.56
Moderately severe	0.42	0.65	0.51
Severe	0.57	1.00	0.62
Average for group	0.53	0.65	0.55

*Doses expressed as milligrams of reserpine or equivalent.

The frequency of depression among patients receiving Rauwolfia could not be correlated with age, sex, known duration and severity of hypertension, nor with associated complicating disease or efficacy of therapy. However, in patients who have experienced a depressive reaction prior to beginning treatment, it seems possible to predict a greater than 50 per cent likelihood of depression occurring during the course of antihypertensive therapy with Rauwolfia. Although most depressions occurred during the first 6 months of treatment with Rauwolfia, a substantial number came on after 1 year. Consequently, constant close observation of the patient is essential during the entire period that Rauwolfia is being administered. While the relation of the dose to the depression was not striking, no depressions were observed among patients receiving 0.2 mg. of reserpine per day or less. However, it is possible that even this amount is not "safe" under all circumstances.

It is our belief that hypertensive patients with a prior history of mental depression almost certainly should not receive prolonged therapy with any preparation of Rauwolfia serpentina. In addition the risk of depression

is sufficiently great among patients without such a history that the use of these drugs should be undertaken only after a careful evaluation of the patient's need for treatment and a thorough appraisal of his emotional status. Even then it is probable that, when other methods of antihypertensive therapy are available and control the blood pressure adequately without deleterious side effects, Rauwolfia preparations should not be used at all.

Summary

A review was made of 387 resident patients with arterial hypertension who were treated at the Mayo Clinic during the years 1954 and 1955. It was found that of 202 patients who were treated with some form of Rauwolfia serpentina, 53 (26 per cent) experienced a depressive reaction. This was moderately severe or severe in 21 persons (10 per cent). In contrast a comparable control group of 185 hypertensive patients who received no antihypertensive medication produced only 9 instances (5 per cent) of depression with 6 (3 per cent) being classed as moderately severe or severe. The evidence did not indicate any relationship of depression to severity of hypertension, to drugs other than Rauwolfia, or to the efficacy of treatment in lowering blood pressure. In addition no correlation could be found between depression and the age or sex of the patient, nor with any complicating disease.

Depression occurred in more than half of those persons who had a history of depression prior to beginning treatment with Rauwolfia and in almost a fourth of the patients without such a history. The dose of Rauwolfia tolerated by different individuals varied, but no depressions were observed in patients taking less than 0.2 mg. of reserpine daily. Although 32 (60 per cent) of the 53 depressive reactions occurred within the first 6 months after treatment with Rauwolfia was begun, 6 (11 per cent) came on after 1 year of treatment. Patients taking Rauwolfia serpentina, whether as whole root extract, alseroxylon fraction, or reserpine, require close observation indefinitely for any evidence of mental depression.

In view of the frequency and severity of depressive reactions among hypertensive patients treated with Rauwolfia, the physician must evaluate the indications for use of this drug with extreme care and whenever possible avoid its use altogether.

Summario in Interlingua

Esseva facite un revista del casos de 387 residente patientes con hypertension arterial qui esseva tractate al Clinica Mayo durante le annos 1954 e 1955. Esseva trovate que le gruppo de 202 patientes tractate con le un o le altere forma de Rauwolfia serpentina includeva 53 (i.e. 26 pro cento) qui experientiava un reaction depressori. Iste reaction esseva moderatemente sever o sever in 21 casos (i.e. 10 pro cento). Per contrasto con isto, un comparabile gruppo de 185 patientes hypertensive recipiente nulle medication antihypertensive includeva solmente 9 casos de depression (i.e. 5 pro cento), e solmente 6 de istos (i.e. 3 pro cento) poteva esser classificate como moderatemente sever o sever. Le datos non revela un relation inter depression e severitate del hypertension, inter depression e drogas altere que Rauwolfia, o inter depression e le efficacia del tractamento antihypertensive. In plus, nulle correlation esseva constatabile inter depression e le etate o sexo del patiente o inter depression e le presentia de un morbo complicatori.

Depression occurreva in plus que un medietate del subjectos con un historia de depression ante le institution del tractamento con Rauwolfia e in quasi un quarto del patientes sin un tal historia. Le doses de Rauwolfia tolerate per differente individuos variava, sed nulle depression esseva observate in patientes qui recipeva minus que 0.2 mg de reserpina per die. Ben que 32 del 53 reactiones depressori (i.e. 60 pro cento) occurreva intra le prime 6 menses post le institution del tractamento con Rauwolfia, 6 (i.e. 11 pro cento) se declarava post un anno de tractamento. Patientes a qui Rouwolfia serpentina es administrate—non importa si in le forma de extracto ab le radice total, in le forma del fraction alseroxylona, o in le forma de reserpina—r

iire le plus stricte observation—e isto in-finitemente—pro le presentia de manifesta-ones de depression mental.

Viste le frequentia e le severitate del reac-ones depressori in patientes hypertensive actate con Rauwolfia, le medico debe evalu-r le indicationes pro le uso de iste droga con rande attention, e in tanto que possibile ille ebe evitar le uso del droga completemente.

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The Forces Needed to Evoke Sounds from Cardiac Tissues, and the Attenuation of Heart Sounds

By WILLIAM DOCK, M.D.

There has been no study of the efficiency of any sound-producing system. Here there is a description of a device that records the force of each pull applied to a valve segment or strip of myocardium while the sound evoked is recorded. The relation of force to sound intensity, and the attenuation of sounds in air, blood, and ventricular and chest walls provide some quantitative data on a neglected phase of cardiac physiology.

A BRIEF SERIES of experiments[1] showed that relatively little force is required to evoke loud sounds when leaflets and chordae of the cardiac valves are drawn taut under water, although large forces are required to evoke sounds from strips of heart muscle. In order to obtain some quantitative data on the relation of tensing force to noise, it was necessary to devise a noise-free method for applying and recording forces of varying size. Once it was possible to get consistent records of force and noise with application of a given force, it was easy to compare the sonic potential of various cardiac structures, and the attenuation of sound in blood, air, myocardium, and the tissues of the chest wall.

METHOD

Records were made on a Sanborn Twin-Beam galvanometer. The acoustic elements were calibrated with a Maico audiometer.

An SRA-Type C strain gage, bonded to a steel spring, provided the data on forces applied to the tissues. A 12-volt alternating current was applied to a variable Wheatstone bridge, in which the strain gage was one element. This arrangement gave an output of 3.1 mv. (± 0.1 mv.) per 100 Gm. when forces of 25 to 400 Gm. weights were applied to the spring, in the device shown in figure 1. A Lucite tank, 14 by 18 cm. and 20 cm. deep, was used for immersion of the tissues. A stethoscope head with watertight diaphragm was fixed to the wall of the tank, with a tube leading through the wall to the microphone. Tank and microphone rested on foam rubber 5 cm. deep to insulate them from vibrations in the building. The apparatus was set up in a quiet room, not used for any other purpose.

As seen in figure 1, a heart valve cusp, *V*, is fastened at its annular margin to a balsa block firmly set in an 800-Gm. lead weight, *W*. This is done outside the water bath, with the beam, *E*, and attached fixtures are suspended so that the papillary muscles, *P*, can be fastened to the small balsa paddle, *D*. This paddle is firmly fastened to the spring, *S*, on one half of which the strain gage is bonded. The spring has its ends set in the prongs of the paddle, *C*, and the handle passes through a hole in the beam, *E*, to which it is fixed by an axle, *A*, on which the paddle swings freely. A long enterostomy clamp is used to lift the weight with one hand, while the beam is lifted from its support with the other. The device is thus transferred to the water-bath, and the beam slipped into place on the axle, *F*, which can be adjusted to any desired height above the bath. The depth of water is sufficient to cover the stethoscope diaphragm and the lower half of paddle, *D*. A lead weight, *L*, is placed on the beam, drawing the valve taut, and the axle is adjusted so that the beam is horizontal. Then the balsa block, *B*, on another adjustable mount, is placed so that it stops the descent of the left arm of the beam when the right end is lifted by hand. The usual setting permits 1 cm. descent of the axle, *A*, thus allowing 1 cm. of slack in the valve. The axles are steel, tight-fitting, and lubricated with graphite, so that the device generates no sound. The block, *B*, is faced with 3 mm. of foam rubber so that contact between it and the beam is almost noiseless. This contact occurs only in the interval between tests.

The distance from *A* to *F* is 6 cm. When a lead weight, as a tight-fitting rider, is placed on the right arm 3 cm. from the axle, the force rais

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g the paddle is half that of the weight, which lls half the distance the paddle rises when the am is released after being pressed against *B*. nce the riders vary from 25 to 200 Gm. and n be placed at 3, 6, 9, or 12 cm., force can be ried over a wide range. The beam is balanced a lead weight built into the right end, but fine justment, to compensate for the buoyancy of e partly immersed lower paddle, is made with a all weight close to *F*, on either side as needed, st before starting a series of tests. A metal int, at the right end of the beam, is touched th a finger to raise the weighted beam. It is leased when the other end rests on *B*. Lifting d release are repeated 6 to 8 times for each cord, made at a paper speed of 2.5 or 7.5 cm./sec.

When attenuation of sounds in ventricular or thoracic wall is tested, disks of tissue more than twice the size of the stethoscopic diaphragm were held over the diaphragm by a wire ring that pressed the edges of the tissue against the wall of the tank. Only light pressure and support were needed and the pressure on the diaphragm was no greater than water pressure in ordinary recording.

Calibration

The strain gage was tested by lifting the weights attached by a short cord to the edge of the lower paddle. The voltage change, 3.15 mv. (± 0.1 mv.) per 100 Gm., remained constant over the range 25 to 400 Gm. and over 5 months of testing. Thus the voltage output was 1 mv./30,000 dynes. The records were made with a galvanometer sensitivity of 2 mm./mv., and in the figures 1-mm. deflection of the trace equals 15,000 dynes.

The Sanborn microphone was first tested with the standard stethoscope diaphragm attached directly as for heart sound recording. The normal adult gives a first apical heart sound record with a deflection of 8 to 12 mm. with the logarithmic amplifying circuit and the sensitivity control at "6." Deflections produced by heart sounds, by sounds elicited from valves under water, and by sounds from an audiometer were compared at various settings of the amplifier, from 4 to 8. With any given sound, if the deflection at setting 4 be taken as 1, the deflection at 5 is 3, at 6 it is 8, at 7 it is 20, and at 8 it is 35. All of the tests on valves were recorded with the logarithmic circuit at settings in the range of 4 to 7, and the deflections were reduced to equivalent deflections at 5 by multiplying the deflection at 4 by 8, that at 5 by 2.7, and the deflection at 7 by 0.4.

When the earphone of the Maico audiometer was applied to the Sanborn diaphragm, with the amplifier at 6 the deflection was 11.6 mm. for 7 db. at 128 c.p.s., 14.6 mm. at 256 c.p.s., and 4 mm. at 500 c.p.s. Thus the first sound is equivalent to 60 to 70 db. at the 125-cycle level; this also is the sound intensity of the unit, the sone, used by students of hearing and sound engineering.

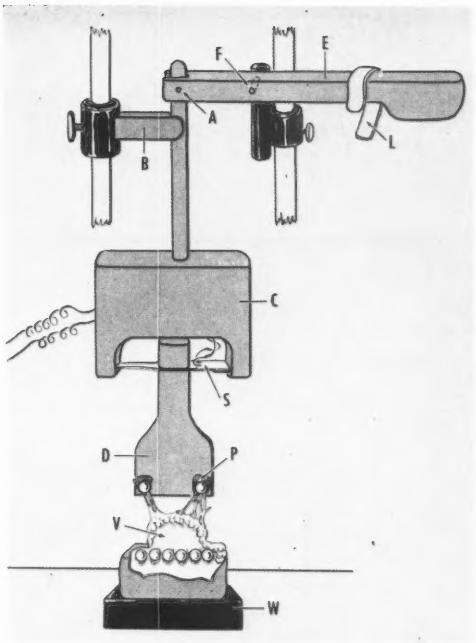

Fig. 1. Devices used to record force applied to cardiac structures.

When the bone conduction unit of the Maico audiometer was applied to the Sanborn diaphragm, the "10 db." setting gave a 6.4-mm. deflection at 125 c.p.s., 7.6 at 250 c.p.s., and 1.4 at 500 c.p.s. When the diaphragm and tube connection used in the tank were tested with the bone conduction unit, "20 db." at 125 c.p.s. gave a 7.2-mm. deflection. This result means that a pure sustained 125 c.p.s. tone, recorded through a tube from the tank, is attenuated to less than half of what it would be if recorded with the Sanborn diaphragm directly attached to the microphone. However, when the microphone, tube, and diaphragm from the tank were used to record apical heart sounds of a normal subject, the peak amplitude was only 15 per cent smaller than when the Sanborn diaphragm was applied at the apex.

With both types of Maico stimulator and over the range of 10 to 80 db., the Sanborn microphone with the logarithmic amplifier shows a 3-fold increase in deflection amplitude for a 10 db., and a 10-fold increase with a 20 db., increase in sound. The audiometric decibel is based on sound intensity levels as related to the logarithm of the

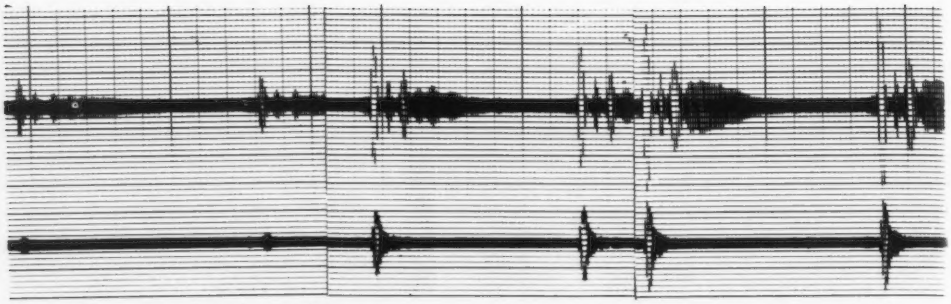

FIG. 2. In this and other figures, *upper* pattern is the strain-gage record of tension applied to the valve (1 mm. = 15,000 dynes); *lower* is sound. From a complete anterior mitral leaflet with 2 papillary tips and many chordae. At this setting (5) of amplifier, a "normal" first sound gives a deflection of 4 mm. This demonstrates increase in sound with increase in force tensing entire cusp-chordae system.

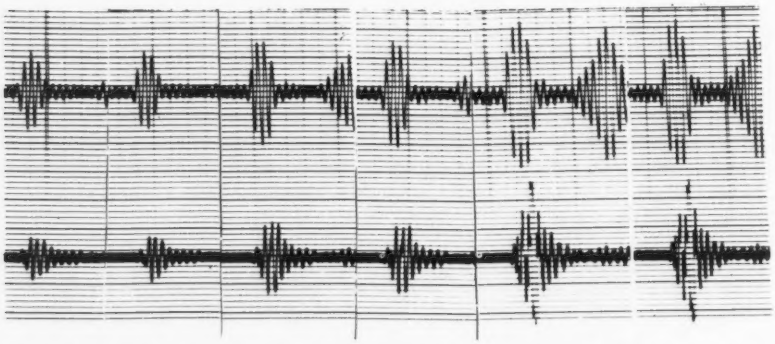

FIG. 3. High speed recording, from 2-chordae preparation; posterior tricuspid leaflet. From a normal man, age 20, killed violently. Recorded at 4.5 setting.

square of the pressure acting on the eardrum.[2] The equation is

Sound intensity in decibels =

$$20 \log_{10} \frac{\text{sound pressure}}{0.0002 \text{ dynes/cm.}^2}$$

Thus a 3.1 increase in sound pressure equals 10 db., a 10-fold increase 20 db., a 31-fold increase 30 db., 100-fold increase 40 db., etc. Since the "logarithmic" amplifier units of the Sanborn phonocardiogram give a galvanometer deflection, as described above, 3 times as large for 10 db., and 10 times as large for each 20 db. increase in sound at the 125 to 250 c.p.s. range, the response is linear with sound pressure, and not with the logarithm of the ratio of sound pressure to the standard threshold of 0.0002 dynes/cm.[2]. The unit records sound pressure, not decibels. The latter can be derived from the data when needed to show the relation of increased sound to increased force applied to a valve.

Loudness, on the sone scale, is very different from decibels or sound intensity.[2, p. 207] A rise from 60 to 75 db. at 125 c.p.s. gives a 10-fold increase in loudness. Thus, at levels close to the normal heart sound, an increase of 15 db. in sound or of 5-fold increase in the Sanborn signal would correspond with a 10-fold increase in loudness. Therefore, in our graphic records, changes in amplitude of sound signal are less than apparent loudness would be to an auditor.

RESULTS

Relation of Tensing Force to Sound Intensity

When an entire cusp with all its chordae and tips of papillary muscles is tensed with increasing force, the sound evoked becomes louder. Changes in quality and duration also are evident. A series of such force-sound curves from different valves shows very wide variation. This is due to the great variation in number and points of attachment of the chordae, especially with posterior mitral

cusps or any of the tricuspid cusps. If one uses only 1 papillary tip, with 2 chordae to the edge of the leaflet, tensing only the central segment of the cusp, the sonic properties of different valves become less variable. But, as increasing force is applied, changes in pattern as well as intensity do occur, and breaks in the curve are seen when force is plotted against sound. These are shown in figures 2 and 3, selected from the experiments on which table 1 and figure 4 are based.

When the sound intensity in decibels is plotted against maximum force recorded during tensing these cusp and chordae preparations, a straight line can be drawn through the center of the group lines (fig. 4). This line intercepts the 60-db. level at 100,000 dynes, and the 80-db. level at 300,000 dynes. On the average, sound intensity increased 10-fold with a 3-fold increase in force above that required to evoke noise equal to the normal first sound.

As is evident in figure 4 the lines of force-sound relations intercept the zero force level at relatively high sound levels. This means that the straight line relationship is valid only in the range of 100,000 to 500,000 dynes. In the group of mitral cusps with 2 chordae, the range of zero force interceptions varied from 37,000 to 58,000 dynes, and $\Delta F/\Delta S$ varied from 6,000 to 13,500 dynes/db. The lowest values for both were in a cusp from a young normal heart; the highest, in the cusp from a middle-aged hypertensive subject. The ratio of sound to force rises relatively rapidly from 10,000 to 50,000 dynes and is almost linear from 80,000 dynes up to 800,000 dynes.

Relative Sonic Potentialities of Cardiac Tissues

When entire cusps, with the complex of chordae and 2 to 4 papillary tips, are tested, it is found that sounds of a given intensity are more easily evoked from anterior mitral leaflets than from other preparations, and that the posterior tricuspid cusp also is relatively easily set into audible vibration. The shorter cusps and many chordae of the elements that make up the rest of the atrioventricular valve ring appear to be much less effective vibrators. But, as shown in table 1 and figure 4, the simple elements taken from all leaflets are comparable in their sonic responses to tensing. When a posterior mitral cusp giving a small response is cut down to provide such a simple preparation, a louder noise may be given by the small portion of the valve when the same tension is applied. And when the chordae only or the leaflet only is mounted in the testing device, the same tension may evoke almost as much noise from the small portion as from the entire segment from papillary tip to annulus fibrosus. Splitting up of tension between many chordae and parts of cusps with little probability that all will be equally tensed at the same instant appears to make the sound evoked from some entire valves less intense than from simple elements. Apparently the force per fiber, rather than the size of the fibrous structure being tensed, is a very important factor in determining the sonic behavior of the atrioventricular valves when tensed in our device. The force applied to a pair of chordae is also applied to the segment attached to it. Undoubtedly the difficulty in

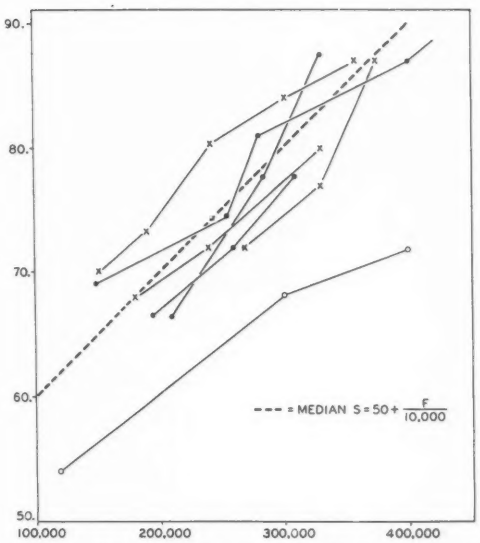

FIG. 4. Figure based on data in table 1, with sound intensity (S) in decibels as *ordinate*, force (F) in dynes as *abscissa*. ○, from intact anterior mitral leaflet; ●, from 2-chordae preparations of anterior mitral leaflets; X, from similar tricuspid posterior leaflet preparations.

TABLE 1.—*Sonic Responses to Tensing Forces on Valve Leaflets*

Valve leaflet	Sound pressure*	Forces (dynes)
1. Anterior mitral	2.1	195,000
Age 28	4.0	270,000
	7.8	310,000
2. Anterior mitral	2.1	210,000
Age 35	7.5	285,000
Hypertensive	24.0	330,000
3. Anterior mitral	2.8	150,000
Age 62	5.5	255,000
	11.2	280,000
	22.4	400,000
	27.5	420,000
4. Anterior mitral	0.5	120,000
Age 24	2.6	300,000
(Fig. 2)	3.9	400,000
Posterior mitral	4.1	270,000
Age 48	7.0	330,000
	22.0	375,000
Posterior tricuspid	2.5	180,000
Age 20	4.0	240,000
	10.0	330,000
Posterior tricuspid	3.2	150,000
Age 62	4.8	190,000
	10.4	240,000
	16.4	300,000
	22.4	360,000

*Sound pressure 1 is that of average apical first sound and gives a sound intensity of 60 db. Sound pressure 10 gives an intensity of 80 db.

adjusting a series of papillary tips on the paddle so that tension will be applied equally to all is an important factor in impairing the sonic response of the complex leaflets. Slight shifts in position of the paddle in relation to the lead-weighted balsa block may markedly change loudness, duration, and character of the sound evoked, although in any given position each preparation gave a constant pattern.

The strain-gage records show that the entire system of paddles, beam, and weight goes into a low-frequency oscillation, or "bounces" when a valve or other fibrous structure is suddenly drawn taut. The pattern of this oscillation depends on the natural frequency of the weighted system and on the viscosity an resiliency of the tissue being tested. Thu in figure 5, the relatively stiff and simple a terior mitral valve swiftly decelerates the ri of the paddle, pulls the weighted arm up an releases all force on the spring for 0.08 se The delicate, many-stranded posterior leafl produces slower deceleration of the paddl with small rapid bounces and a long series audible vibrations rather than a sharp sna These vibrations may be due to taut chord rubbing against each other during t "bounce." The strip of interventricular se tum is so viscous that deceleration of t paddle is gradual, no real bounce occurs, a no audible vibration is evoked by a force times that which produces from the anteri mitral leaflet a sharp sound as loud as t normal apical first sound.

The testing device, intended merely to apply variable forces, or the same force repeatedly, was thus useful in showing how fast the force was absorbed. The type of "bounce" gave some idea of the resilience and viscosity of the tissues. Often the rebound would evoke a sound, as in figure 5.

As had been previously noted,[1, fig. 19, no. 4] strips of fat-free parietal pericardium the size of a mitral leaflet can be set into audible vibration, and so can small strips of atrial wall, or the entire membranous interatrial septum of an occasional heart. Faint sounds can be elicited by great force from ventricular walls (figs. 5 and 6), in strips 2 cm. wide, but not from a whole lateral wall of a normal heart.

Attenuation of Sounds in Blood and in Ventricular and Chest Walls

With the use of anterior mitral cusp and chordae tendineae, the relative sound production in air, water, and whole blood could be recorded. The valve system was not touched between tests, and force records in these comparative tests were constant. The most striking difference was the extremely feeble sound produced when valves were tensed in air as compared with water (fig. 7). The sound intensity is 20 times greater, with the mic-

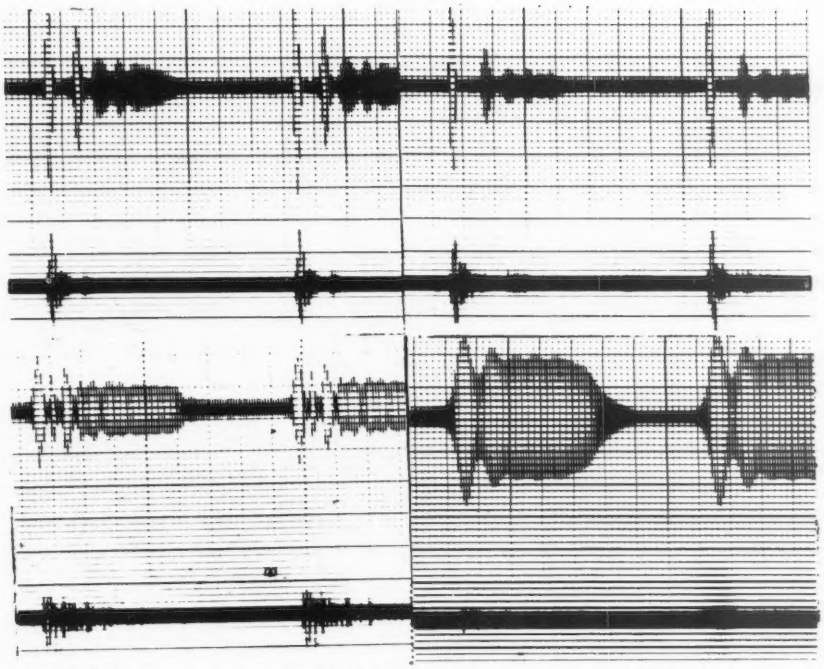

FIG. 5. *Left upper,* anterior mitral leaflet; *lower left,* posterior mitral leaflet, both at setting 5, beam weighted with 100 Gm. at 3 cm. *Right upper,* same mitral leaflet, beam weighted with 50 Gm. at 3 cm.; *right lower,* strip of ventricular septum, weight 200 Gm. at 6 cm.; both at setting 6. Normal heart, 300 Gm.

phone 2.5 cm. from the leaflet, in water than in air, and the sound is much sharper. The attenuation of sound in blood is slight. In the most marked example (valve to diaphragm, 5 cm.) the decrease in intensity in blood was 30 per cent. In most records it is evident that high-frequency vibrations are much more reduced than those under 100 c.p.s. The corpuscles may damp the vibrations of the fibers, or merely attenuate transmission, like snow flakes in air.

The most marked attenuation in passing through a normal right ventricular wall held in front of the microphone was 20 per cent, but with hypertrophied left ventricular wall, in rigor and 3 to 4 cm. thick, sound intensity fell 65 per cent in one experiment and 45 to 50 per cent in 3 others, passing through the ventricular walls of hypertensive subjects. In figure 8 are shown the results of interposing intact chest wall, with 2 cm. of fat and skin and 1.5 cm. of rib cage and pleura, between the valve and the diaphragm of the phonocardiograph. The loss of intensity in the entire wall taken from the left precordial region over the heart was 65 per cent. When the skin and fat were tested, the loss was 20 per cent; when the ribs, muscle, and pleura were interposed, the loss was over 40 per cent. Five other tests with chest wall gave a minimal attenuation of 42 and a maximal of 81 per cent. All these tests, as those with attenuation in blood, show changes in sound pattern, as well as in its intensity, so that attenuation varies with frequency.

It must be re-emphasized that these percentage changes in the Sanborn signal correspond with percentage change in sound pressure, not in decibels or loudness. The rise of 5-fold pressure on removing the chest wall means a 15 db. rise in sound, and about a 10-fold increase in loudness. The sound produced by

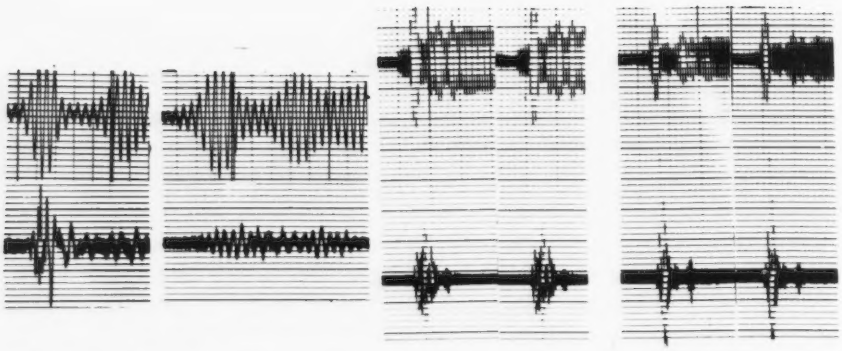

FIG. 6. From *left to right*, interatrial septum, interventricular septum, both at 6; mitral anterior leaflet from annulus to line of closure; same, chordae from line of closure to papillary muscle, recorded at 5. Weight, 200 Gm. at 3 cm., except for chordae, 100 Gm. at 3 cm. A 650 Gm. heart.

a given force acting on the valve in water would be reduced in a large heart, 30 per cent by blood, 50 per cent by the ventricular wall, and 50 per cent by the chest wall, or a total attenuation of 80 per cent on the average. With the maximal observed losses this might be 95 per cent, or 25 db. A loud sound would become only 2.5 per cent as loud with this attenuation, since 1 sone is 25 db. down from 40 sones.[2, p. 208, figs. 8, 2] Whenever air-filled lung is interposed, even larger losses of sound transmission occur, since small air cells provide optimal sound-proofing, and valve sounds are markedly attenuated when produced and transmitted in air.

DISCUSSION

In our experiments the valve elements were tensed, as they are in the body, in a fluid medium. The force necessary to evoke sounds of varying intensity was measured in water, as well as the attenuation experienced when sounds are produced in and transmitted through air or blood, and when they pass through the ventricular walls and the thoracic wall. It was found that the sound evoked when force was applied to a segment of a cusp, or even to 2 chordae, might be faint, as loud as, or, rarely, even louder than when the same force was applied to the whole leaflet with all its chordae. A force of about 100,000 dynes is needed to evoke from a pair of chordae and attached segment of a valve leaflet a sound equal to the apical first sound. To allow for the attenuation in blood, ventricular and thoracic walls, sound pressures 4 to 10 times greater must be evoked, and the force needed may be 180 000 to 300,000 dynes.

At the time the first heart sound occurs the difference in pressure on the 2 sides of the valve must be small, for the cusps have been floating freely in blood and there is a common chamber until the valves are drawn taut. All the force available for causing the sound must come from the arrest of the mass of blood moving from the ventricle toward the atrium, and from the contraction of papillary muscles, drawing the ends of the chordae tendineae in the opposite direction.

In our experiments, the valve elements were stretched in a straight line, and the annular edge also was stretched straight. In life the annular edge is curved, the cusps fill out in ares, like a ship's sail in the wind, and only the chordae are straight, like the rigging holding a flying sail. The chordae to the center of leaflets are not properly tensed in the device we use, and the entire system would have to be redesigned to fasten the cusp to a circular base and adjust all papillary tips to exert equal tension on the chordae to all parts of the cusp, as they do in the living heart. It is quite probable that a careful re-examination with such a device would reveal a higher production of sound per dyne of force applied to the valve. Yet the fact that a given force ap

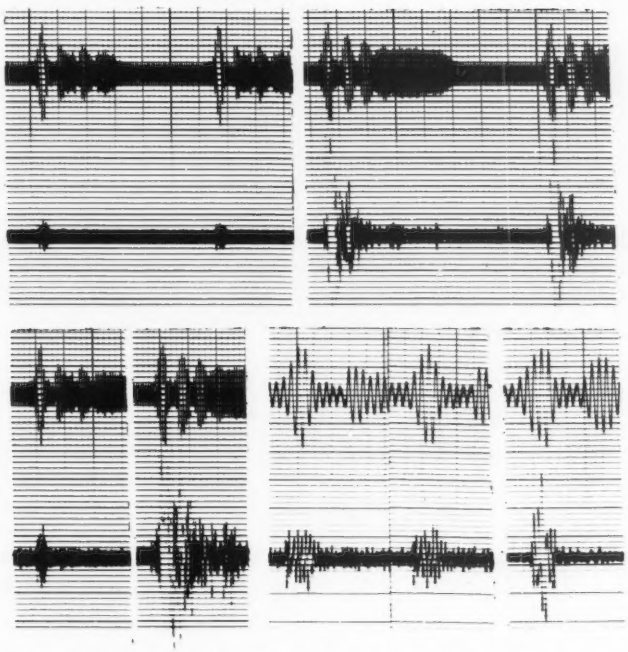

FIG. 7. *Upper row,* anterior mitral leaflet in air on *left,* in water on *right,* both recorded at 6. Below, *left to right,* in air, in water, both at 7; in air, at 7; in water, at 4. A valve tensed under water 2.5 cm. from stethoscope diaphragm produces far more noise than when tensed in air by same force.

plied to very small segments of valves, or to chordae alone, evokes sounds almost as loud as when it is applied to an entire leaflet, makes us believe that the general relationship of sound to force, and of the force needed to evoke the heart sounds from atrioventricular valves, is given by experiments such as these.

Proper positioning will lead to sharper sounds, for it will prevent friction of chordae against other chordae, and insure instantaneous tensing of all units. Thus maximal sound production from an entire valve will be similar to that when simple units of 2 chordae and a small segment of leaflet are tensed, as in the experiments on which table 1 and figure 3 are based.

When short segments of fibers are tensed, as in the semilunar cusps or the portion of mitral valve from annulus to line of adhesion tensed in a mitral snap, the pitch is higher, the sound is sharp, but the intensity may be very great. In the semilunar cusps, all the force is supplied by the inertia of the mass of arterial blood that is accelerated back toward the ventricle, since there is no motion of the points of attachment of valve margins. In the stenotic mitral valve, the mass of blood moving toward the ventricle is large, and a large pressure difference may develop between atrium and ventricle as the membrane moves from its end-systolic to its diastolic position.

Since the ventricular walls require very large tensing forces to produce audible vibrations, it is doubtful if they contribute to the heart sounds. Certainly the tension developed during systole causes little or no sound, as has been shown by the delay in the first sound in mitral stenosis, even though fiber tension in the wall rises to more than double that attained when a normal heart produces a first sound. The arrest of blood entering in diastole may tense chordae,[3-6] in mitral insufficiency with shortened cusps and chordae, but there is not enough inertial force to tense the ventricular wall forcibly enough to cause a sound.

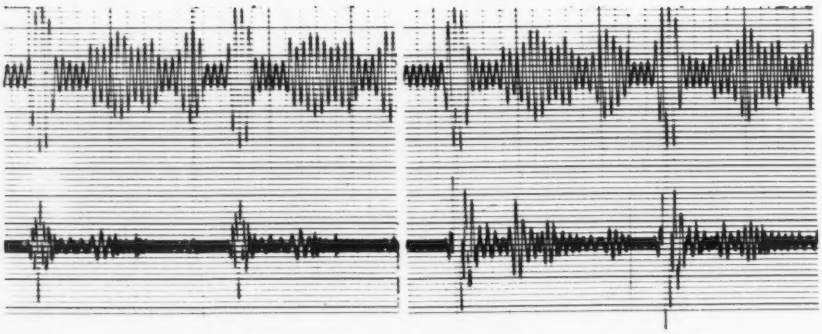

FIG. 8. Anterior mitral leaflet. On *left*, entire anterior chest wall, pleura to skin, interposed between valve and microphone; on *right*, chest wall removed; recorded at 5.

The effect of ventricular wall in attenuating sound may be of some importance in explaining the location of areas of optimal audibility of sounds. All the valves are located close together, with interlocking fibrous rings, but first sounds and gallop sounds are loudest close to the apex of the left ventricle, while opening mitral snaps are loudest somewhat medial to this and even in the third left interspace next to the sternal border. The aortic second sound is loudest close to the sternum on the right at the same level, and tricuspid sounds close to the sternum in the fourth or fifth left interspace.

The left ventricle is thinnest at the apex,[7] and approaches the chest wall most closely at this point, so that attenuation of the mitral first sound is least over the apex. In gallop and first sounds, the chordae are tensed, and as they are closer to the apex probably provide more sound than do the cusps. In mitral snap the noise of the cusps is less well transmitted into the apical region, but by shaking of the roots of the aorta and pulmonary artery, as well as by transmission into the dilated left atrium, it may reach the chest wall close to the sternum with less attenuation in traversing these thin structures. The pulmonic and aortic sounds are heard best where the bends of the arteries in which they arise approach the chest wall most closely, for there is probably minimal attenuation of sound in fluid-filled semi-rigid tubes.

It is remarkable how feeble are the sounds evoked when valves are tensed in air as compared with those heard when the same force is applied to valves immersed in water. This shows how far astray speculation could lead even so fine an investigator as Magendie. He rejected Rouanet's thesis that the first sound was valvular, in spite of the ingenious experimental support Rouanet had given it. Rouanet, in one series of experiments, had obtained sounds from membranes tensed in air, and Magendie objected that what happened in air was not likely to occur in fluid-filled ventricles.[8] Actually, the sound would have been far louder if Magendie had repeated Rouanet's experiment with the membranes and stethoscope tip under water.

A surprising outcome of these experiments was the finding of a linear relation between sound intensity in decibels and the increase in peak force developed in tensing a cusp or chorda. The general equation is $S = x \frac{(F\text{-}n)}{(n)}$ where S is sound intensity, F is force in dynes, n, the force in dynes needed to evoke a sound of intensity 1, and x the constant for each valve. We tried to find other experiments relating sound to force, but failed to find any. Intensity of sound in relation to force has not interested experimental or theoretical physicists. There are good studies of sounds in tanks,[9, vol. 2, p. 217] which would aid in performing this type of experiment in echo-free chambers. But in the classic texts on physics and on sound[9-11] we found nothing on the relation of sound intensity to the force applied to strings or to air columns. There appear

b o studies of efficiency of sound production, gi ing relation between force and sound, when va ious types of cords or membranes are suddly drawn taut or struck when tensed.

Summary

A quantitative method of comparing a sound due to tensing cusps of valves, or other cardiac structures, and the peak force applied, shows that efficiency of sound production increases at higher levels of force. A straight line describes the relation of the logarithm of sound intensity to increase in force, above that needed to evoke a sound equal in intensity to a standard such as the first sound heart at the precordium on auscultation. The relatively stiff valves of older people or those with elevated intraventricular pressures give off louder sounds, for a given force, than the delicate structures of young normal subjects. Very large forces are needed to evoke audible sounds from strips of ventricular muscle and no such force levels occur in living animals.

Attenuation of heart sounds in air (and hence in aerated lung) is great. Attenuation in blood, ventricular wall, and chest wall is such that 70 to 95 per cent of sound intensity must be lost between the mitral cusps and the precordium even when the apex is in contact with chest wall.

Acknowledgment

It is a pleasure to express my appreciation of the courtesy of the Medical Examiner's Office, the Department of Pathology, in providing space and facilities, and especially to Drs. G. W. Ruger, F. S. Wedding, and E. L. White for their help in making this work possible.

Summario in Interlingua

Un methodo quantitative pro comparar un sono producite per tensification de cuspides valvular o de altere structuras cardiac con le fortia maximal applicate monstra que le efficientia del production de sonos es plus alte al plus alte nivellos de fortia. Un linea recte describe le relation inter le logarithmos del intensitates de sono e le augmentos de fortia supra le nivello requirite pro evocar un sono equal in intensitate a un standard de base, per exemplo le prime sono cardiac que es audite al precordio in le auscultation. Le relativemente inelastic valvulas de subjectos de etate avantiate e le valvulas de subjectos con elevate pressiones intraventricular produce plus marcate sonos pro un date nivello de fortia que le delicate structuras de juvene subjectos normal. Multo grande fortias es requirite pro evocar audibile sonos ab pecias de musculo ventricular, e nulle tal nivellos de fortia occurre in animales in vivo.

Le attenuation de sonos cardiac in aere—e ergo in pulmones aerate—es grande. Le attenuation in sanguine, pariete ventricular, e pariete thoracic es si pronunciate que inter 70 e 95 pro cento del intensitate del sono debe esser perdite inter le cuspides mitral e le precordio, mesmo quando le apice es in contacto con le pariete thoracic.

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The Role of Vessel Tone in Maintaining Pulmonary Vascular Resistance in Patients with Mitral Stenosis

By HERBERT J. SEMLER, M.D., JOHN T. SHEPHERD, M.D., D.Sc., AND EARL H. WOOD, M.D., PH.D.

Changes in pulmonary vascular (arteriolar) resistance were estimated in 58 patients with mitral stenosis following mitral valvotomy and during exercise. Evidence is presented that changes in "resistance" reflect active changes in the caliber of the vessels due to alteration in their smooth muscle tone, valvotomy being followed by a decrease in tone and exercise by an increase.

IT IS well known that patients with mitral stenosis have medial hypertrophy of the pulmonary arteries, that a muscular media develops in the arterioles,[1-4] and that these histologic changes often are accompanied by an increased resistance to blood flow through the vessels of the lungs.[5] Many attempts have been made to define the mechanism of this increased resistance with the use of adrenergic and ganglionic blocking agents.[6-9] The conflicting nature of the conclusions emphasizes the difficulty in interpreting the results. This is mainly due to the fact that the potent action of these drugs on the systemic circulation makes it difficult to decide whether the changes in the pulmonary circulation are actively or passively induced. The recent use of acetylcholine injected into the pulmonary artery in such a concentration that it is inactivated before reaching the left side of the heart has demonstrated that the high pulmonary vascular resistance in mitral stenosis is at least partly functional;[10] that is, tone is present in the smooth muscle of the pulmonary vessels and this contributes to the pulmonary hypertension.

In the present paper, some of the factors are examined that may be concerned in the maintenance of this tone.

METHODS

The hemodynamic data on 58 adult patients were analyzed. All patients had mitral stenosis as the predominant valvular lesion, as judged by clinical and laboratory findings, and this was confirmed in the majority of cases at the time of mitral valvotomy. There were 42 women and 16 men, aged 18 to 53 years, with an average age of 34 years for the women and 38 years for the men. Any patient having a systemic blood pressure higher than 140 mm. Hg systolic and 90 mm. diastolic was not included in this report.

Intravascular pressures were recorded by strain-gage manometers, the zero reference point being midchest at the level of the third interspace on the sternum with the patient supine. The cardiac output was determined by the Fick principle. The rate of consumption of oxygen was measured by collecting expired air for 5 minutes and analyzing it immediately by the Haldane method; blood samples from the pulmonary and radial arteries withdrawn midway during the collection of expired air were analyzed for their oxygen content in duplicate by the method of Van Slyke and Neill.[11] The oxygen capacity of hemoglobin was measured by the method of Sendroy,[12] with the modification of Roughton, Darling, and Root.[13] Midway during the collection of the blood samples, a record of pulmonary and radial artery pressures was obtained that was considered to represent the resting state. The catheter tip was then advanced into the "wedge" position of either peripheral lung field and the pressure was measured.

For the exercise studies the catheter tip was left in the pulmonary arterial wedge position. The patient exercised in the supine position on a bicycle ergometer,[14] which was positioned at the end of the fluoroscopy table. The revolutions of the ergometer caused the deflection of a galvanometer needle, which was visible to the patient; the deflection was recorded photographically by means of a second galvanometer. By the patient's maintaining the needle at a predetermined position a constant speed of rotation of the exercycle was achieved. After an average of 3½ minutes from the start of exercise, a record of pulmonary arterial wedge and radial artery pressures was obtained.

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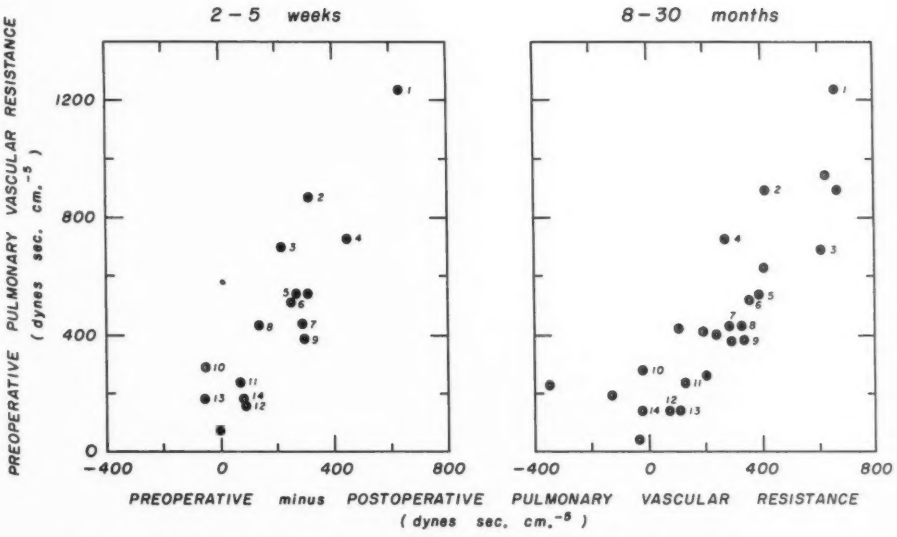


FIG. 1. Changes in pulmonary vascular resistance in 25 patients with mitral stenosis at 2 to 5 weeks (*left*) and 8 to 30 months (*right*) following mitral valvotomy. Each dot represents an individual patient; dots with numbers represent the patients studied on both occasions after operation.

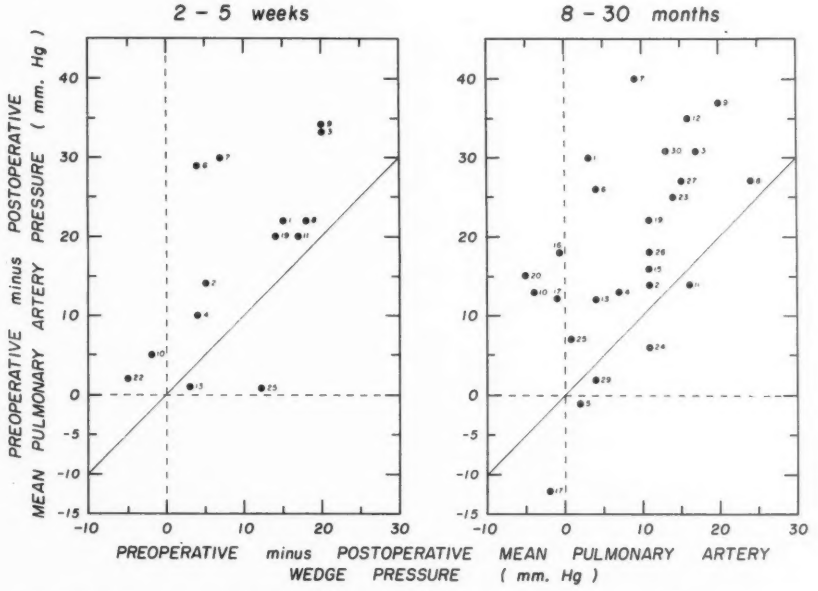


FIG. 2. Relation between change in mean pulmonary artery and change in mean pulmonary arterial wedge pressures 2 to 5 weeks (*left*) and 8 to 30 months (*right*) following mitral valvotomy. Dots and accompanying numbers as described for figure 1.

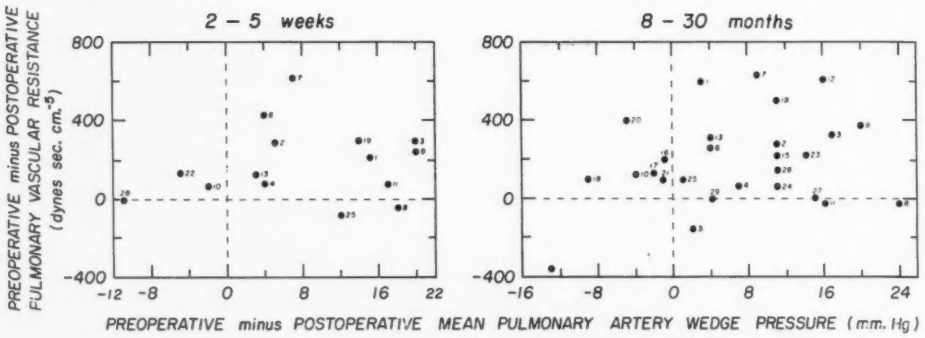


FIG. 3. Comparison between change in pulmonary vascular resistance and change in mean pulmonary arterial wedge pressure in mitral stenosis 2 to 5 weeks (*left*) and 8 to 30 months (*right*) following mitral valvotomy. Dots and accompanying numbers as described for figure 1.

The catheter tip was then withdrawn to the main pulmonary artery; after recording of the pressure, blood samples were taken simultaneously from the pulmonary and radial arteries. During this sampling period expired air was collected; its volume was measured, and the gases were analyzed by the Haldane method.

The following formulas were used in calculations:

$$\text{total pulmonary resistance} = \frac{\bar{P}_{PA} \times 1{,}332}{Q}$$

$$\text{pulmonary vascular resistance (arteriolar)} = \frac{(\bar{P}_{PA} - \bar{P}_{LA}) \times 1{,}332}{Q}$$

$$\text{total systemic resistance} = \frac{\bar{P}_{SA} \times 1{,}332}{Q}$$

In these formulas

$\bar{P}$ = mean pressure in mm. Hg
Q = the blood flow, i.e., cardiac output in milliliters per second
PA = pulmonary artery
LA = left atrium
SA = systemic artery

Mean pressures were obtained by planimetry. The mean pulmonary arterial wedge pressure was assumed to equal the left atrial pressure.[15-18] Data obtained from this laboratory[19] on a group of 22 normal persons studied under similar conditions were included for purposes of comparison.

RESULTS

Effect of Mitral Valvotomy on Pulmonary Vascular Resistance. Figure 1 shows the changes that had taken place in pulmonary vascular resistance 2 to 5 weeks and 8 to 30 months after mitral valvotomy. Those patients with the highest pulmonary vascular resistance before operation had the greatest decrease after operation. This decrease occurred within 2 to 5 weeks and no further important change had taken place many months later.

There can be little doubt that valvotomy resulted in decreased resistance to blood flow across the pulmonary vascular bed consequent to dilatation of pulmonary vessels. First, the pulmonary artery pressure decreased more than the pulmonary arterial wedge pressure; hence the pulmonary blood flow was maintained by a smaller perfusion pressure (fig. 2). Second, if the pulmonary vessels had behaved as a passive system, lowering of the left atrial pressure by valvotomy would tend to increase the pulmonary vascular resistance by reducing the transmural pressure of the pulmonary vessels and hence the distention of the pulmonary vascular bed.[20, 21] On the contrary, lowering the left atrial pressure caused a reduction in resistance (fig. 3).

This dilatation of the pulmonary vessels was most likely the result of a decrease in vessel tone and not a passive phenomenon due to a decrease in extravascular compression of pulmonary vessels by edema consequent on the lowering of the capillary pressure by valvotomy. Haddy and Campbell[22] have shown in dogs that the calculated pulmonary resistance remains low when pulmonary edema is present, and they suggested that acute

edema of the lungs per se may not be an important factor in determining the caliber of the vessel. Again, if this had been the explanation of the decreased resistance, a more definite relationship might have been expected between the changes in pulmonary vascular resistance and the changes in wedge (left atrial) pressure than that which is apparent in figure 3.

The Effect of Exercise on Pulmonary Vascular Resistance. The pulmonary vascular resistance with the patient at rest and during exercise plotted against the mean pulmonary artery pressure at rest in 34 patients with mitral stenosis is shown in figure 4. Many of the patients, and especially those with a pulmonary artery mean pressure in excess of 30 mm. Hg, showed an increase in resistance during exercise. Similar findings have been reported by Eliasch [23] Tompkins,[24] and Holling and Venner.[25] In suggesting that the increase in resistance was a consequence of a vasoconstriction, the previous arguments apply. The pulmonary artery pressure increased more than the pulmonary arterial wedge pressure (fig. 5), so that there was an increase in the pressure gradient across the vascular bed of the lung. The increase in pulmonary arterial wedge (left atrial) pressure would tend to distend the vessels with a consequent fall in resistance. In spite of this the pulmonary vascular resistance was increased (fig. 6). If we assume that this increased resistance was unlikely to be due entirely to pulmonary edema, then these results are compatible with the thesis that an active vasoconstriction had occurred.

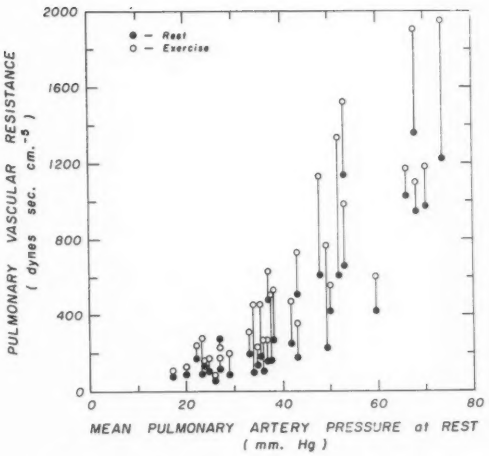
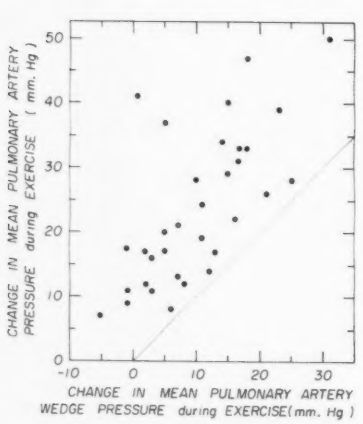


FIG. 4. Comparison of the pulmonary vascular resistance with the patient at rest and during exercise with the pulmonary artery mean pressure at rest in 34 patients with mitral stenosis.

DISCUSSION

Deduction of changes in vessel caliber from values obtained from vascular resistance equations must be made with caution. The pulmonary vascular bed, subject as it is to pulsatile changes in blood flow,[26] alterations in heart rate and stroke volume, is a complex system in which pressure fluctuations occur at variable frequencies and amplitudes. The equation used to determine resistance, however, applies strictly to a system in which there is laminar flow and a steady pressure. Resistance to flow through the pulmonary vascular bed is a function of the ratio of the pressure gradient between the pulmonary artery and the left atrium (perfusion pressure) to the volume of flow through the system. Despite the complexity of this system, under conditions where volume of flow and frequency change little and intrathoracic pressure is unchanged, an increase in perfusion pressure is a good indication that the caliber of the "resistance" vessels has decreased, particularly if pressure in the pulmonary vein remains the same or is increased. Under the opposite conditions it can be assumed that the caliber of the "resistance" vessels has increased, particularly if pressure in the pulmonary vein is the same or is decreased.

Considering first the results of valvotomy in cases in which the described conditions are fulfilled, there can be little doubt that the drop in resistance indicates an increase in vessel caliber, and that this increase in caliber is consequent on lowered pressure somewhere in the pulmonary system, including the left atrium. If the reduction in pulmonary vascular resistance present 2 to 5 weeks after mitral valvotomy occurred too early to be



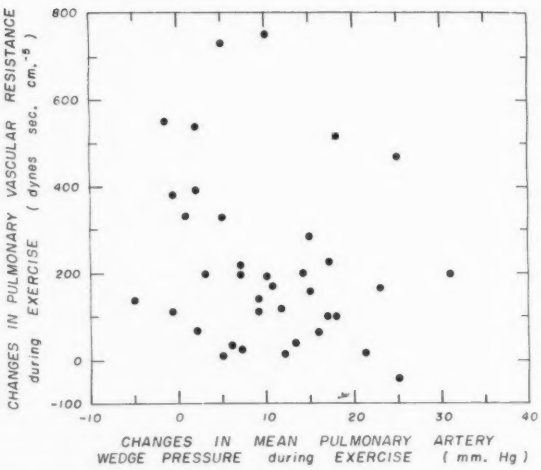


FIG. 5 *Left.* Change in pulmonary artery and pulmonary arterial wedge pressure during exercise in mitral stenosis.

FIG. 6 *Right.* Comparison of changes in pulmonary vascular resistance and pulmonary arterial wedge pressure during exercise in patients with mitral stenosis.

explained by the regression of histopathologic changes in the vessel walls, then it was most likely due to vasodilatation of the pulmonary resistance vessels consequent on reduced tone of the smooth muscle. Consistent with this are the results of experiments by Ferguson and Varco,[27] who found that such a pathologic regression is a comparatively slow process; unfortunately, however, complete observations of pulmonary artery pressure, left atrial pressure, and flow just before and after mitral valvotomy are not available.

The finding of increased vascular resistance with exercise is harder to evaluate. It is difficult to deduce changes in caliber by means of the simple resistance formula when definite changes occur in frequency and pressure fluctuations in the system coincident with the changes in heart rate and respiration. There is, however, some support to the thesis that the vessel caliber is decreased. The increase in left atrial pressure during exercise would tend to cause a passive increase in vessel caliber. This occurs in dogs when mitral stenosis is created,[28] so that the pulmonary vascular pressure gradient decreases as the pressure is elevated in the pulmonary veins. In human beings, the situation is different. The pressure gradient between the pulmonary artery and the left atrium increases with exercise. Thus the resistance changes are contrary to those expected on mechanical grounds, which is a good indication that they are due to alterations in vessel tone opposing the distending force.

Blood vessels are distensible structures and their caliber depends on their pressure-volume characteristics. The effective distending pressure is the transmural pressure, which is the intravascular minus the extravascular pressure. If blood vessels behaved as a viscoelastic system, increases in this pressure would cause an increase in vessel caliber until the limits of elasticity were reached. This would be modified, however, by the degree of tone in the smooth muscle of the vessel wall. The normal pulmonary vessels in the adult dog have sufficient smooth muscle to be capable of strong constriction,[29] and Cournand[30] and Fritts and his associates[31] have shown that tone is present in normal pulmonary vessels. The evidence already presented demonstrates that the increase in pulmonary vascular resistance associated with mitral stenosis ca-

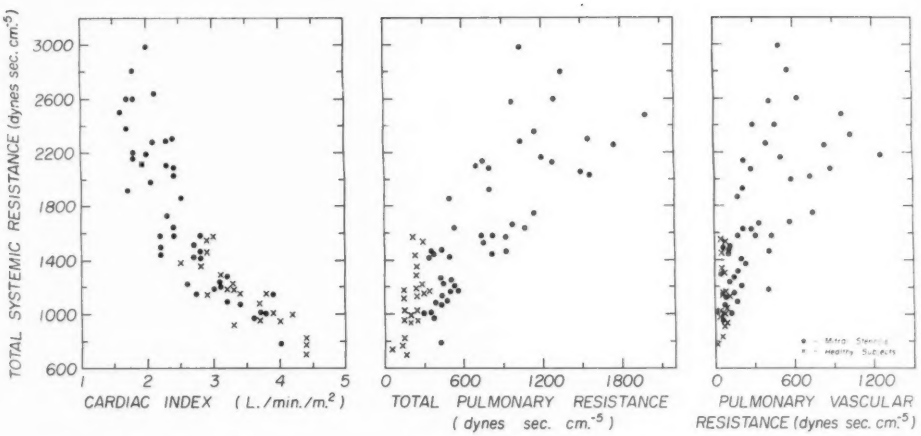


FIG. 7. Relation of systemic resistance to cardiac index and pulmonary resistance during rest in patients with mitral stenosis and in healthy persons.

not result solely from organic changes in the blood vessels altering their viscoelastic properties, but that it must be due in part to increased tone in the smooth muscle. This emphasizes again Wood's concept of the important role played by vessel tone in mitral stenosis.[10]

In a consideration of mechanisms that might alter the tone of the pulmonary vessels in mitral stenosis one might first see whether or not the stimulus could originate outside the thorax. For example, a relationship was noted between the systemic resistance and the cardiac index during rest (fig. 7). As the index decreased, the systemic resistance increased. There was also a relationship between the systemic resistance and the total pulmonary and pulmonary vascular resistances (fig. 7). It was likely that the increased systemic resistance with decreasing output was brought about through the baroreceptors in the carotid and aortic sinuses so that the systemic blood pressure was maintained. If this were so, reflex effects from the baroreceptors to the pulmonary vessels were also possible. However, Daly and Daly[32] in a recent paper suggested that the changes in the pulmonary circulation with baroreceptor activity were most likely passive and not active. Furthermore, Lee and associates[33] used the Valsalva maneuver and did not find evidence for reflex pulmonary vasoconstriction.

Changes in pulmonary vessel caliber can result from changes in alveolar oxygen tension.[34, 35] When the pulmonary vascular resistance during rest and during exercise was plotted against the oxygen saturation of mixed venous blood, there was a suggestion that the less the oxygen saturation of blood in the pulmonary artery the greater the resistance (fig. 8). A similar correlation has also been shown by Holling and Venner.[25] This would be compatible with the evidence that breathing low-oxygen mixtures can cause constriction of pulmonary vessels in mitral stenosis.[36] While the relationship between the changes in pulmonary vascular resistance following valvotomy and the changes in oxygen saturation of mixed venous blood was not consistent (fig. 8), the possibility still exists that lowered oxygen saturation of mixed venous blood may be a factor in the increased pulmonary vascular resistance in mitral stenosis.

Recent studies on the human systemic circulation have shown the importance of changes in transmural pressure in modifying vessel tone.[37-40] The present observations suggest that changes in pressure somewhere in the pulmonary vascular bed or the left atrium may be a stimulus capable of regulating tone

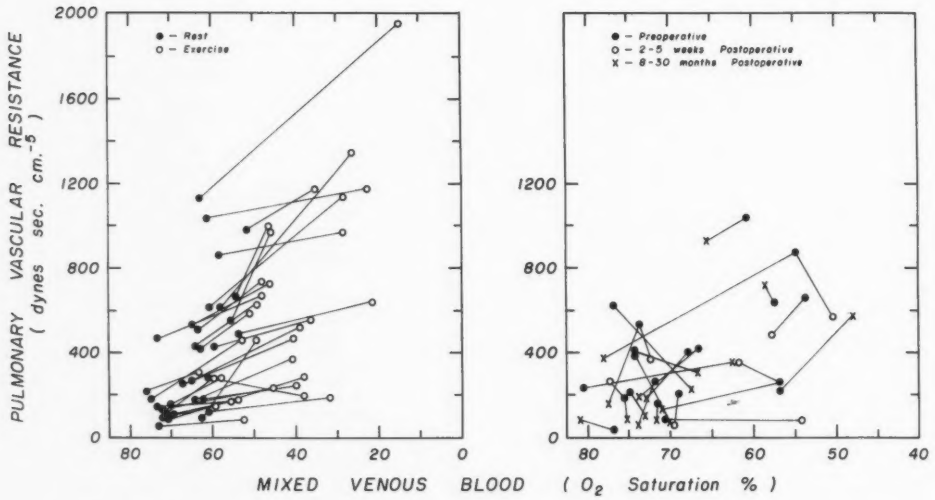


FIG. 8. Comparison of the changes in pulmonary vascular resistance and mixed venous blood oxygen saturation per cent during exercise (*left*) and following mitral valvotomy (*right*) in patients with mitral stenosis.

in the pulmonary vessels. These alterations in tone could be effected either through a local non-nervous response of the smooth muscle to the changes in pressure such as has been described for the systemic vessels,[38, 41] or to local nervous reflexes from the increase in pulmonary venous or left atrial pressure.[42, 43] Ferencz and Dammann,[44] from their microscopic study of the lungs of patients with congenital heart disease in whom there was an obstruction of pulmonary venous drainage, suggested that the latter may be an important factor in the development of pulmonary arterial narrowing.

SUMMARY

The pulmonary vascular (arteriolar) resistance was measured in 58 patients with predominant mitral stenosis during exercise and 2 to 5 weeks and 8 to 30 months after mitral valvotomy.

Mitral valvotomy was followed by a decrease in resistance that was directly proportional to the magnitude of resistance before operation. Many patients showed an increase in resistance during exercise and especially those with a mean pulmonary artery pressure while resting in excess of 30 mm. Hg.

Evidence is presented that these changes in "resistance" represent active changes in the caliber of the pulmonary vessels due to alteration in their smooth muscle tone, with valvotomy causing a decrease in tone and exercise causing an increase in tone.

The thesis is advanced that changes in pressure somewhere in the pulmonary vascular bed, including the left atrium, may be a stimulus capable of regulating tone in the pulmonary vessels of patients with mitral stenosis.

ACKNOWLEDGMENT

The authors wish to thank Drs. H. B. Burchell, H. F. Helmholz, Jr., W. T. Lyons, R. L. Parker, R. D. Pruitt, H. J. C. Swan, and R. G. Tompkins for their helpful cooperation. The mitral valvotomies were performed by Drs. F. H. Ellis, Jr., and J. W. Kirklin, who kindly informed the authors of their operative findings.

SUMMARIO IN INTERLINGUA

Le resistentia pulmono-vascular (i.e. arteriolar) esseva mesurate in 58 patientes con predominante stenosis mitral, durante exercitio e 2 a 5 septimanas e 8 a 30 menses post valvotomia mitral.

Valvotomia esseva sequite per un reduction de resistentia, directemente proportional al

magnitude del resistentia ante le operation. Multe patientes manifestava un augmento de resistentia durante exercitio. Isto esseva specialmente ver in le caso del patientes qui habeva un pression pulmono-arterial medie in stato de reposo de plus que 30 mm de Hg.

Es presentate datos que indica que iste alterationes del "resistentia" representa alterationes active in le calibre del vasos pulmonar in consequentia de un alteration in le tono de los musculos lisie. In iste situation, valvotomia causa un reduction de tono, e exercitio causa un augmento de tono.

Es formulate le these que alterationes de pression in le un o le altere loco del vasculatura pulmonar—incluse le atrio sinistre—es un stimulo capace a regular le tono in le vasos pulmonar de patientes con stenosis mitral.

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Blood Pressure Studies in Rural and Urban Groups in Delhi

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Very little data exist about blood pressure levels in Indians although it is generally believed that they are lower than among Western peoples. There also seems to be an impression that hypertension is rarer among poor Eastern populations. This study was carried out on 1,132 persons of poor economic status and 224 persons of good social class in Delhi. The results showed some striking differences between the two groups and from Western figures. Factors influencing the blood pressure levels, such as age and body weight, were also evaluated.

DURING the course of an investigation into the incidence of hypertension and atherosclerosis, dietary fat intake, and blood cholesterol levels in Delhi State,[1] the blood pressures of a large number of persons of both urban and rural groups, totaling 1,132, were recorded. From these data it was possible to determine the range of normal blood pressures in Indians in Delhi in these social groups and to assess the incidence of hypertension in them. There have been very few studies on the blood pressure range in normal Indians in the past; the only previous large-scale study was that of Dubey.[2] These data obtained in Delhi might fill a gap in our knowledge of blood pressure ranges in India.

The definition of hypertension as given by the New York Heart Association[3] was accepted although it was realized that the levels of 140 mm. systolic and 90 mm. diastolic as normal were arbitrary and that wide variations from these figures were found in presumably normal subjects.[4] A diagnosis of hypertension for purposes of calculating the incidence was made only after careful assessment of the blood pressure figures and other cardiovascular data such as the electrocardiogram, x-rays of the chest, and urinalysis.

Material and Methods

Two types of population were studied:

1. *Low-Socioeconomic Groups*

A. A large rural group of 648 persons, 267 men and 381 women.

B. An industrial group composed of 484 men from a large mill in Delhi.

2. *High-Socioeconomic Groups*

A. *Men.* Men from various occupational groups of high-socioeconomic status were selected, the total number being 200. There were 53 doctors, 23 business executives, 29 engineers, 22 Sikhs (a religious sect which was chosen for the survey because of a reported high consumption of fat), 15 hockey players, 3 army officers, 1 lawyer, 39 government officials, and 15 medical students.

B. *Women.* There was only 1 group of women in the high-economic class: 24 women medical students of the Lady Hardinge Medical College.

All these persons were subjected to a routine history and complete physical examination including electrocardiography, as stated in our previous paper.[1] The blood pressures were taken according to the recommendations of the Committees of the American Heart Association and Cardiac Society of Great Britain and Ireland[5] under as basal conditions as possible. All the readings were recorded in the sitting position.

Results

The results were grouped under the following 3 heads:

1. Rural and Industrial Groups (Low-Socioeconomic Status)

In the case of the rural and industrial workers it was possible, owing to the large number of cases, to study the variations in blood pressures in relation to age and body weight. These findings have been summarized in tables 1 to 6 and figures 1, 2, and 3.

2. High Socioeconomic Groups

A. *Men.* The blood pressures in the 200 individuals in this group were also analyzed with regard to age and body weight, although

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TABLE 1.—*Variation in Blood Pressure with Age in Najafgarh Rural Population (Men)*

Mean age (yr.) ±S.D., range of age	No. of cases	Mean body wt. (lb.) ±S.D., range of body wt.	Mean sys. B.P. (mm. Hg) ±S.D., range of sys. B.P.	Mean dias. B.P. (mm. Hg) ±S.D., range of dias. B.P.	Cases with B.P. over 140/90 mm. Hg	
					No.	% age
16.2 ± 2.4 10 — 19	42	101.8 ± 20.0 44 — 138	111.1 ± 13.3 90 — 140	70.9 ± 10.5 40 — 90	Nil	Nil
23.7 ± 3.0 20 — 29	107	117.4 ± 16.7 82 — 154	116.0 ± 10.0 94 — 150	78.2 ± 9.3 60 — 100	4	3.7
33.3 ± 1.6 30 — 39	54	119.9 ± 17.3 88 — 172	117.6 ± 11.3 96 — 150	78.2 ± 8.0 50 — 100	1	1.8
42 ± 2.5 40 — 49	42	120.3 ± 24.9 90 — 180	117.3 ± 13.6 88 — 156	79.6 ± 11.7 50 — 100	3	7.2
52.9 ± 3 50 — 59	13	126.6 ± 23.4 95 — 174	117.5 ± 18.7 90 — 156	78.8 ± 11.9 60 — 100	2	15.4
62.2 ± 1.9 60 — 69	9	98.8 ± 15.4 90 — 124	116.4 ± 8.2 108 — 130	77.1 ± 7.8 60 — 90	Nil	Nil

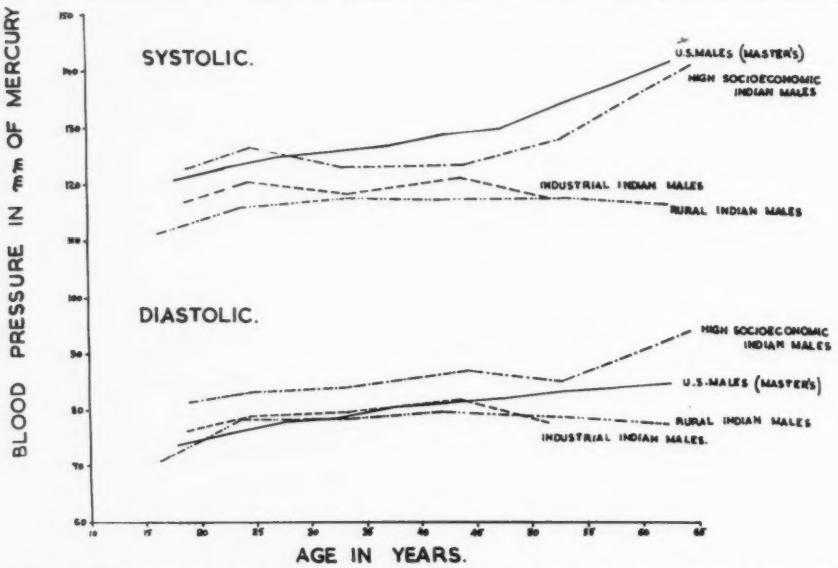

FIG. 1. Variations of blood pressure with age, in males. Indian and U.S. figures compared.

the small number of cases in this group unavoidably increased the statistical error (tables 7 and 8 and figs. 1, 2, and 3).

B. *Women.* Both the blood pressure and the age in this group fluctuated very little from the mean (table 9).

3. Comparison between High-and Low-Socioeconomic Groups

Comparisons were made between the blood pressures, systolic and diastolic, in the high- and low socioeconomic groups (figs. 1, 2, and 3) and between the weights and blood pressures in individuals matched for age and height individually from the high-socioeconomic groups and the rural population (table 9). The rise of body weight with age in both sexes in the 2 groups is given in tables 1, 3, 5, and 7 and in figure 4.

1. Low-Socioeconomic Groups.

A. *Men.* Since the trends in the rural and industrial workers were similar, the results in these 2 groups were considered together. The body weights in these 2 groups ranged from 65 to 195 pounds, the lower figures being obtained in the rural men. The average body weight per inch of height was 1.8 pounds for the rural and 1.87 pounds for the industrial

TABLE 2.—*Variation in Blood Pressure with Body Weight in Najafgarh Rural Population (Men)*

Mean body wt. (lb.) ±S.D., range of body wt.	No. of cases	Mean sys. B.P. (mm. Hg) ±S.D., range of sys. B.P.	Mean dias. B.P. (mm. Hg) ±S.D., range of dias. B.P.
77.1 ± 9.6 65 — 89	10	104.4 ± 11.2 90 — 124	69.0 ± 11.2 50 — 90
93.2 ± 3.2 90 — 99	30	113.0 ± 10.1 90 — 124	77.8 ± 11.6 60 — 90
104.7 ± 3.2 100 — 109	41	111.6 ± 9.8 90 — 130	75.1 ± 7.9 60 — 90
113.7 ± 2.8 110 — 119	57	117.5 ± 10.3 88 — 156	76.3 ± 9.6 50 — 100
123.2 ± 3.1 120 — 129	59	117.8 ± 11.2 100 — 150	78.3 ± 8.1 60 — 90
133.3 ± 3.2 130 — 139	17	115.6 ± 9.0 100 — 130	78.6 ± 8.1 60 — 90
155.6 ±10.9 140 — 180	26	127.8 ± 11.1 108 — 156	83.8 ± 5.3 70 — 100

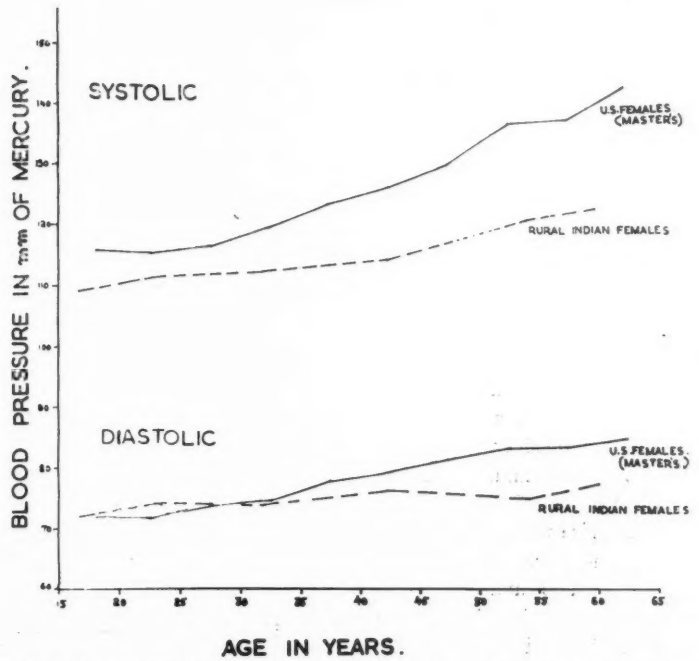

FIG. 2. Variations of blood pressure with age, in females. Indian and U.S. figures compared.

group. These figures were low compared to those for Western men of similar medium frames: 2.1 to 2.4 pounds. For their heights 7.3 per cent of the industrial workers and 3.8 per cent of the rural men were overweight.

Variation with Age (Tables 1 and 5 and Fig. 1). In both groups the lowest systolic and diastolic blood pressures were recorded in the second and the highest in the fifth decade. There was no consistent rise in blood pressure with age except between the second and third decades, a feature noted incidentally in all the groups studied. The rise with age did not appear significant, being not more than 6 mm. Hg in systolic and 9 mm. Hg in diastolic blood pressures over 4 decades.

TABLE 3.—*Variation in Blood Pressure with Age in Najafgarh Rural Population (Women)*

Mean age (yr.) ±S.D., range of age	No. of cases	Mean body wt. (lb.) ±S.D., range of body wt.	Mean sys. B.P. (mm. Hg) ±S.D., range of sys. B.P.	Mean dias. B.P. (mm. Hg) ±S.D., range of dias. B.P.	Cases with B.P. over 140/90 mm. Hg No.	% age
16.7 ± 2.3 10 — 19	32	97.6 ± 21.2 50 — 134	109.1 ± 13.5 86 — 156	72.0 ± 9.2 56 — 90	Nil	Nil
22.9 ± 2.6 20 — 29	197	106.3 ± 15.8 74 — 192	111.8 ± 9.8 90 — 144	74.1 ± 7.6 60 — 100	2	1.01
32.0 ± 2.3 30 — 39	97	111.3 ± 18.3 80 — 180	112.4 ± 10.6 90 — 144	73.7 ± 7.6 55 — 95	2	2.0
42.2 ± 2.9 40 — 49	35	109.2 ± 20.6 94 — 140	114.5 ± 13 90 — 150	76.4 ± 9.4 54 — 90	1	2.9
54.2 ± 4.0 50 — 59	16	100.0 ± 27.8 84 — 152	121.3 ± 20.7 90 — 170	75.0 ± 12.3 50 — 100	3	18.7
60 60 and over	4	95.5 76 — 142	123.5 110 — 160	77.5 60 — 100	1	25

Variation with Body Weight (Tables 2 and 6 and Fig. 3). There was a steady rise of blood pressure both systolic and diastolic with body weight in both groups, the highest and lowest blood pressures being recorded with the highest and lowest body weights respectively. The maximum rise in blood pressures with body weight was 13 mm. Hg.

B. *Rural Women.* The body weight of this group ranged from 66 to 176 pounds, the average weight per inch of height being 1.7 pounds. The standard figures for Western women of the same frame are given as 1.9 to 2.1 pounds.[6] There were 29 women (5.5 per cent) who were overweight for their heights.

Variation with Age (Table 3 and Fig. 2). There was a consistent rise of systolic blood pressure with age, being 14 mm. higher in the seventh (123 mm.) than in the second (109 mm.) decade; this rise was probably significant. Over the same period the rise in diastolic blood pressure was 5 mm. Hg. There was a sharp rise of systolic blood pressure between the second and third and between the fifth and sixth decades.

Variation with Body Weight (Table 4 and Fig. 3). As in the case of the men, the rise of blood pressure with body weight was a steady one, the highest and lowest pressures being recorded with the highest and lowest body weights. The maximum rise was 10 mm. Hg.

Incidence of Hypertension. Tables 3 and 7 show that the percentage of cases showing a blood pressure of over 140/90 mm. Hg increased with the decades, being highest in the seventh. Among both men and women there were only 2 out of 1,132 with true hypertension (1 man and 1 woman in the rural group and none in the industrial group) giving an incidence of 0.17 per cent.

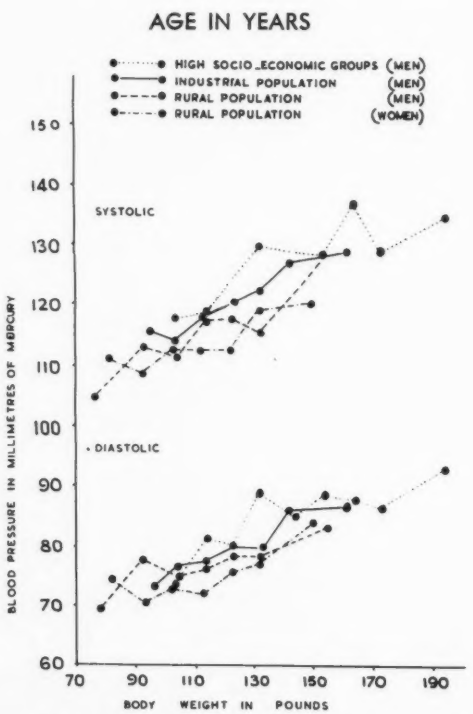

FIG. 3. Variations in blood pressure with body weight.

TABLE 4.—*Variation in Blood Pressure with Body Weight in Najafgarh Rural Population (Women)*

Mean body wt. (lb.) ±S.D., range of body wt.	No. of cases	Mean sys. B.P. (mm. Hg) ±S.D., range of sys. B.P.	Mean dias. B.P. (mm. Hg) ±S.D., range of dias. B.P.
81.6 ± 5.5 66 — 89	29	111.0 ± 11.5 90 — 154	74.8 ± 10.5 50 — 100
93 ± 2.6 90 — 99	63	108.8 ± 9.9 90 — 140	70.9 ± 7.5 54 — 90
103.2 ± 3.2 100 — 109	76	112.3 ± 8.9 90 — 144	74.0 ± 8.3 60 — 96
112.3 ± 2.4 110 — 119	66	112.6 ± 10.8 90 — 170	72.9 ± 7.7 54 — 100
122.3 ± 2.8 120 — 129	37	112.5 ± 9.5 90 — 140	75.6 ± 7.6 60 — 90
132.3 ± 2.6 130 — 139	22	119.0 ± 10.9 100 — 150	77.6 ± 7.3 60 — 90
150.6 ±11.5 140 — 176	11	120.8 ± 9.2 110 — 160	84.4 ± 7.6 70 — 100

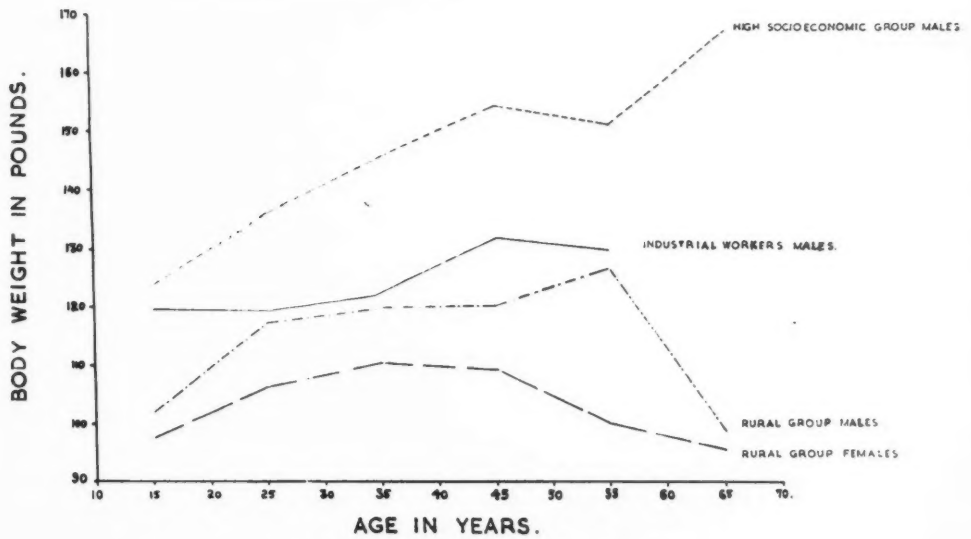

FIG. 4. Variations in body weight with age.

2. High-Socioeconomic Groups.

A. *Men.* Body weight in the high socioeconomic groups ranged from 100 to 208 pounds, and 57 persons (28.5 per cent) were overweight as compared to the ideal weights given by the Metropolitan Life Insurance Statistical Bureau.[6] The average weight per inch of height was 2.01 pounds, the range being from 2.3 among the doctors to 1.77 pounds among the sportsmen.

Variation with Age (Table 7 and Fig. 1). There was a significant, 18-mm. rise of systolic pressure between the second (122 mm. Hg) and seventh (140 mm. Hg) decades. The diastolic pressure rose 13 mm. in the same period. Both systolic and diastolic pressures rose sharply in the seventh decade, 13 and 10 mm. respectively. The rise in systolic pressure between 20 to 29 years was present in this group also.

Variation with Body Weight (Table 8 and Fig. 3). The rise in both systolic and diastolic blood pressures was certainly a steadier one with body weight than with age.

TABLE 5.—*Variation in Blood Pressure with Age in Industrial Population (Men)*

Mean age (yr.) ±S.D., range of age	No. of cases	Mean body wt. (lb.) ±S.D., range of body wt.	Mean sys. B.P. (mm. Hg) ±S.D., range of sys. B.P.	Mean dias. B.P. (mm.Hg) ±S.D., range of dias. B.P.	Cases with B.P. over 140/90 mm. Hg No.	% age
18.6 ± 0.5 18 — 19	9	119.5 ± 12.4 104 — 150	116.8 ± 11.5 100 — 140	76.1 ± 5.1 55 — 90	Nil	Nil
24.5 ± 2.6 20 — 29	236	119.3 ± 13.5 90 — 170	120.2 ± 11.4 90 — 160	78.8 ± 8.7 50 — 96	4	1.7
33.3 ± 2.7 30 — 39	155	122.7 ± 18.4 94 — 192	118.2 ± 11.1 90 — 160	79.5 ± 9.7 50 — 100	8	5.1
43.6 ± 2.3 40 — 49	60	132.1 ± 27.7 88 — 190	121.1 ± 11.3 100 — 160	81.8 ± 9.1 68 — 100	5	8.5
51.5 ± 2.4 50 — 59	24	130.0 ± 9.5 116 — 144	117.9 ± 11.6 110 — 140	77.7 ± 4.6 60 — 100	2	8.3

TABLE 6.—*Variation in Blood Pressure with Body Weight in Industrial Population (Men)*

Mean body wt. (lb.) ±S.D., range of body wt.	No. of cases	Mean sys. B.P. (mm. Hg) ±S.D., range of sys. B.P.	Mean dias. B.P. (mm. Hg) ±S.D., range of dias. B.P.
95.7 ± 3.2 90 — 99	16	115.5 ± 11.6 94 — 150	73.2 ± 11 50 — 90
104.2 ± 1.4 100 — 109	38	114.0 ± 9.5 100 — 160	76.6 ± 8.6 60 — 95
113.5 ± 2.5 110 — 119	73	117.6 ± 10.4 90 — 150	77.7 ± 8.8 50 — 90
124.1 ± 2.7 120 — 129	69	120.2 ± 11.5 90 — 160	80.5 ± 8.2 60 — 100
132.8 ± 3 130 — 139	34	122.5 ± 9.2 108 — 140	79.8 ± 8.3 68 — 90
142.5 ± 2.8 140 — 149	24	127.0 ± 14.6 104 — 160	86.0 ± 8.2 70 — 100
162.3 ±12.5 150 and over	15	128.5 ± 11.9 110 — 150	86.6 ± 7.1 70 — 100

Incidence of Hypertension. The incidence of true hypertension in the high-socioeconomic groups was 2.5 per cent (5 out of 200). The number of cases with blood pressure readings of over 140/90 mm. Hg also increased with the decades (table 7).

B. *Women.* This group comprised a distinct class of women, namely medical students, who were chosen for comparison with the rural females. The average age was only 21 years in this group. The average body weight per inch of height was 1.73 pounds and the range of weight was 92 pounds to 140 pounds. Out of these, 2 students (8.3 per cent) were overweight for their heights. The average systolic and diastolic pressures were 104.9 mm. and 72 mm. respectively. There was not a single case of either true hypertension or blood pressure levels of over 140/90 in this group.

3. Comparison between High- and Low-Socioeconomic Groups

A comparison of the blood pressure readings between the high- and low-socioeconomic groups in figures 1 and 2 showed that in every decade the systolic blood pressure was higher in the high-socioeconomic group than in the low. The difference between the systolic recordings in each decade in the 2 groups varied from 1 to 25 mm. Hg, and was highest in the seventh decade. The diastolic blood pressure was also higher in the high-socioeconomic groups, although the difference did not exceed 10 mm. except in the seventh decade. The blood pressures in the high-socioeconomic groups were significantly higher, both for diastolic and systolic readings, in each decade than those in the rural and industrial groups.

TABLE 7.—*Variation in Blood Pressure with Age in High-Socioeconomic Groups (Men)*

Mean age (yrs.) ±S.D., range of age	No. of cases	Mean body wt. (lb.) ±S.D., range of body wt.	Mean sys. B.P. (mm. Hg) ±S.D., range of sys. B.P.	Mean dias. B.P. (mm.Hg) ±S.D., range of dias. B.P.	Cases with B.P. over 140/90 mm. Hg No.	% age	Low Soc.-eco. groups (men), % age of cases with B.P. over 140/90 mm. Hg
18.89 18 — 19	10	123.9 ± 15.3 118 — 129	122.39 110 — 140	81.19 70 — 90	Nil	Nil	Nil
24.7 ± 2 20 — 29	75	136.1 ± 20.4 102 — 190	126.56 ± 10.2 110 — 150	83.02 ± 8.3 60 — 100	5	6.6	2.3
33.17 ± 2.8 30 — 39	54	146.0 ± 25.7 102 — 178	122.98 ± 8.7 104 — 158	83.66 ± 8.4 70 — 100	4	7.4	4.3
44.25 ± 3.4 40 — 49	32	154.7 ± 21.5 100 — 195	123.4 ± 11.4 100 — 156	86.99 ± 11.7 64 — 105	8	25	7.8
52.85 ± 3.2 50 — 59	17	151.3 ± 24.5 103 — 156	128.02 110 — 146	84.93 70 — 100	Nil	Nil	10.8
64.3 60 — 65	7	167.2 ± 26.0 104 — 208	140.9 120 — 170	94.0 80 — 110	6	85.7	Nil

Variation with Age (Fig. 1). The rise with age was a little more marked in the high-socioeconomic group with regard to both systolic and diastolic blood pressures. Whereas in the rural and industrial groups the maximum fluctuation in systolic blood pressure was 5 to 6 mm. and that in diastolic 5 to 8 mm., in the high-socioeconomic group it was 19 mm. Hg systolic and 13 mm. Hg diastolic.

The rise in systolic blood pressure per decade among the rural men was 1.5 mm. and among the industrial workers 1.6 mm., whereas among the high-income groups it was 3.6 mm. The rise in diastolic blood pressure was 3 mm. for the rural men, 1.6 mm. for the industrial workers, and 2.6 mm. in the high-socioeconomic groups. The systolic rise with age would therefore appear to be more marked in the high-socioeconomic groups.

Variation with Body Weight (Tables 2, 4, and 8, and Fig. 3). The body weight was much higher in the high-socioeconomic group than in the low at every age. Further, there was a steady weight gain with age in the case of the upper classes that was almost absent among the rural and industrial workers. There was a definite fall in weight among both rural men and women after the fifth decade (fig. 4). In all 3 groups the highest blood pressures, both systolic and diastolic, were obtained in those with the highest body weights.

The average increase of blood pressure per pound of body weight was 0.2 to 0.3 mm. for systolic, and 0.2 mm. for diastolic, for all 3 groups, which in itself seemed to suggest that the effect of body weight on blood pressure was a constant one.

A comparison was made between individuals of the high-income groups matched for age and height with those in the rural group. The reason for choosing the rural group was that a large number of individuals were available for accurate matching. A glance at table 9 shows that for the same age and height doctors, engineers, businessmen, and Sikhs have higher body weights (13 to 27 pounds higher) and also higher blood pressures, both systolic and diastolic, than does the rural population. In the case of females, the medical students were compared to the rural women, but here both the body weight and the blood pressures were higher in the rural group. Although the difference in body weight was not considerable (only 2 pounds), there was an 8-mm. difference in the systolic and a 3-mm. difference in the diastolic pressures.

Individuals from the high-socioeconomic groups were also matched for age and weight with those from the low-income groups. There were only 13 persons who could be so matched. Their average age was 29.1 years and average body weight 121.3 pounds. The average blood pressures in the high-income group was 116.1/

TABLE 8.—*Weight and Blood Pressures in High-Socioeconomic Groups (Men)*

Range of wt. (lbs.)	Av. wt. (lbs.) ±S.D.	No. of cases	Mean sys. B.P. (mm. Hg) ± SD., range of sys. B.P.	Mean dias. B.P. (mm. Hg) ± S.D., range of dias. B.P.
100-109	103.75± 2.5	12	117.6 ± 7.2 100 — 130	74.9 ± 6.4 60 — 85
110-119	114.3 ± 3.06	24	118.6 ± 8.1 110 — 136	81.2 ± 7.1 70 — 100
120-129	122.9 ± 3.1	27	124.1 ± 9.5 110 — 140	80.1 ± 7.6 70 — 100
130-139	132.4± 2.8	25	129.7 ±13.8 115 — 150	88.7 ± 8.7 70 — 100
140-149	143.9 ± 3.4	34	128.7 ±12.1 104 — 170	85.4 ±10.1 70 — 110
150-159	154.7 ± 2.4	30	128.3 ±12.2 110 — 158	88.1 ±11 64 — 105
160-169	164.5 ± 3.1	12	136.5 ± 8.2 122 — 150	87.6 ± 6 74 — 95
170-179	173.4 ± 2.6	19	128.2 ±12.4 114 — 160	86.5 ±10.1 70 — 110
180 and over	194.0 ± 9.3	8	134.3 ±18.2 110 — 170	93.0± 9 84 — 110

74.8 mm. Hg and in the low-income group 121.4/81.5 mm. Hg. Only 4 individuals from the 2 groups could be matched for age, weight, and height. The blood pressures were 114.5/77.5 mm. Hg in the high-income and 125/78.5 mm. Hg in the low-income group. It was not possible to match a larger number of persons owing to the great discrepancy in body weight between the 2 social classes.

In these matched individuals the average blood pressures, if anything, were slightly higher in the low-socioeconomic group both for systolic and diastolic readings. It would appear that for the same age, weight, and height, blood pressures were the same in both social classes.

Percentage of Cases with Blood Pressure of over 140/90mm. Hg. Table 7 shows that the number of these cases was higher for every decade except the sixth among the high-income groups.

Incidence of Hypertension. The incidence of hypertension was also higher in the high-income groups, being 2.5 per cent against 0.17 per cent among the low-socioeconomic groups. As stated before, the number of persons in the former group was considerably smaller.

DISCUSSION

The only large-scale survey made in India in the past was that of Dubey (1954), and our results in the low-socioeconomic groups with age and body weight compare with his. He had, however, restricted himself to industrial workers of 1 city. When compared to Western countries, some interesting figures emerge. The average blood pressures resembled the figures given by Boynton and Todd[7] for university students and teachers and those of Robinson and Brucer,[8] up to the age of 40 years only. After the age of 40 years the blood pressure in Robinson and Brucer's series showed a significant rise, whereas in the present series there was none. Our figures were well below those of Gover's[9] both for systolic and diastolic pressures. Our findings as regards the variation in blood pressure with age resemble those of Boynton and Todd inasmuch as the men showed a very small rise with age and the women a sharper and steadier one.

We have also compared the blood pressure levels in all 3 groups with those of Master,[4] who presented the largest survey of this kind ever made. The systolic blood pressures were higher only after the age of 30 years in Master's series, as compared to the Indian high socioeconomic groups. The diastolic blood pressures for these Indians were higher in every decade than for those of the Americans.

In spite of this, the steady rise with age noted in Master's series was not noted in the

TABLE 9.—*Comparison of Weights and Blood Pressures between High- and Low-Socioeconomic Groups (Individuals Matched for Age and Height)*

No. cases	Social status	High-socioeconomic groups			Low-socioeconomic groups		
		Mean wt. (lbs.)	Mean sys. B.P. (mm. Hg)	Mean dias. B.P. (mm. Hg)	Mean wt. (lbs.)	Mean sys. B.P. (mm. Hg)	Mean dias. B.P. (mm. Hg)
14	Doctors	153.7	131.3	88.6	126.7	114.3	75.7
28	Engineers	135.4	121.8	79.2	122.2	113.5	78.7
16	Business executives	144	127.3	85.4	120	122.9	80.9
22	Sikhs	136.3	124.2	82.4	121.2	114.6	75.3
24	Medical students (females)	109.7	104.9	71.8	111.4	112.4	74.8

Indian high-socioeconomic group; this difference perhaps was due to the small number of cases in the present series as compared to Master's.

In the case of the low-socioeconomic groups the systolic blood pressures were higher for every decade in Master's series when compared to either the rural or industrial group. The diastolic blood pressures did not, however, appear to be different until the age of 50, when the levels in Master's series were definitely higher.

The incidence of blood pressures over 140/90 mm. Hg was much lower in all the Indian series for every decade, compared to Master's figures. For the fifth, sixth, and seventh decades the figures for U. S. males were 50 per cent, 60 per cent, and 70 per cent respectively. The percentages for American women were substantially higher than for men. The incidence of true hypertension was harder to compare with Western figures, as those obtainable were for hospital series (as a percentage of all cardiac cases) rather than for selected population groups.

A significant rise was also noted both in systolic and diastolic pressures with body weight in the 2 low-socioeconomic and in the high-socioeconomic groups. The number of individuals in the high-socioeconomic group was one sixth that of the low-socioeconomic groups, a fact which must be taken into account when the rise with body weight is calculated. As stated earlier, the average body weight of the rural and industrial groups was below the optimum, and there were very few individuals who could be considered overweight. In the case of the high-socioeconomic group the body weights of the majority were much higher and fell within the normal range accepted in Western countries.

The fact that when matched for age and height the blood pressures and body weights of persons of the high-socioeconomic groups tended to be higher than those of the low-socioeconomic groups (table 9) also supports this view. Further, when matched for age, weight, and height, the blood pressures in the high-socioeconomic groups were not higher than in the low-socioeconomic groups. This would suggest that body weight was probably the only reason for the significant differences observed in the blood pressures between the 2 groups.

Body weight implies dietary intake, physical activity, and energy expenditure generally. We have not attempted in this study to sort out these various factors. Further, although it is well known that blood pressure is dependent on arm girth, it is not considered of overall importance in the rise of blood pressure with age.[10] The arm girths were not measured in this study.

SUMMARY AND CONCLUSIONS

The blood pressures of 1,132 individuals of low- and 224 individuals of high-income groups were studied. The variation of blood pressure with age and body weight was determined.

In the case of the low-income groups there was practically no rise in systolic and diastolic blood pressures with age, except a constant small rise among women, but there was

a marked rise in both systolic and diastolic blood pressures with increase in body weight.

In the high-socioeconomic groups the body weight and blood pressures, systolic and diastolic, were higher in every decade than in the low-income groups. There was a consistent rise in blood pressures with both age and body weight.

There was a steady weight gain with age among the upper classes that was strikingly absent among the rural and industrial groups.

When compared to Western figures the low-income groups in every decade had lower systolic pressures; the diastolic pressures however, were lower only after the age of 40. The high-income groups had slightly higher systolic pressures up to age 30, after which the American figures were higher. The diastolic readings were higher throughout among the better-class Indians. The incidence of blood pressures over 140/90 was remarkably low among all classes of Indians in all decades.

The conclusion is drawn that the lower blood pressure among the low-income groups was the result of lower body weight and an absence of the weight gain with age, which occurs among Western peoples who are economically better off. We have also not been able to find in this series the sharp acceleration of blood pressure rise, particularly among women, reported by Master et al., after age 40. This again may be due to the absence of weight gain with age in the low-socioeconomic groups.

The incidence of true hypertension in the low-socioeconomic groups was 0.17 per cent and in the high-income group 2.5 per cent.

Summario in Interlingua

Esseva studiate le tension sanguinee de 1.132 individuos de basse e de 224 individuos de elevate stato economic. Le variationes del tension sanguinee con etate e peso corporee esseva determinate.

In le gruppos a basse stato economic, practicamente nulle augmento del pression systolic o diastolic occurreva con le avantiamento del etate, excepte que femininas monstrava un augmento constante. Tamen, in iste gruppos il habeva un marcate augmento del tension systolic e etiam diastolic con le augmento del peso corporee.

In le gruppos a elevate stato economic, le peso corporee e le tension de sanguine, systolic e etiam diastolic, esseva plus alte pro omne decennio del vita que in le gruppos a basse stato economic. Occurreva un augmento systematic in tension de sanguine tanto con le etate como etiam con le peso corporee.

Esseva constatate un continue augmento del peso con le avantiamento del etate in le classes superior. Isto esseva frappantemente absente in le gruppos rural e industrial.

In omne le decennias de etate in le gruppos a basse stato economic, le tension systolic esseva inferior a correspondente cifras reportate in le Occidente. Le mesmo valeva pro le tension diastolic solmente post le etate de quaranta annos. In le gruppos a elevate stato economic, le tension systolic esseva levemente plus alte que le correspondente nivellos reportate in America usque al etate de 30 annos. Post le etate de 30 annos, le cifras reportate in America esseva plus alte. Le tension diastolic esseva plus alte in le gruppos de elevate stato economic in India a omne etates. Le incidentia de tensiones de sanguine de plus que 140/90 esseva remarcabilemente basse in omne classes de omne etates in India.

Le conclusion es que le plus basse tension de sanguine in le gruppos a basse stato economic esseva le resultato del plus basse peso corporee e del absentia del augmento del peso con le avantiamento del etate que occurre inter le occidentales de stato economicamente superior. In plus, nos non ha succedite a trovar, in le presente serie, le acute acceleration del augmento del pression de sanguine que Master et al. ha reportate pro gruppos de etate de plus que 40 annos, specialmente pro femininas. Il es possible que etiam isto se explica per le absentia de augmento de peso con le avantiamento del etate in gruppos a basse stato economic.

Le incidentia de ver hypertension esseva 0,17 pro cento in le gruppos a basse stato economic e 2,5 pro cento in le gruppos a elevate stato economic.

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Cottier, P. T., Weller, J. M., and Hoobler, S. W.: Evaluation of Mecamylamine in the Treatment of Hypertension. J. Lab. & Clin. Med. **50:** 199 (Aug.), 1957.

The status of 31 consecutive hypertensive patients treated as outpatients with mecamylamine and followed for over 3 months was examined. A daily record of standing blood pressure showed a significant drop in over 50 per cent. Approximately one third showed normal daily standing blood pressures. In approximately 20 per cent medication had to be discontinued because of distressing side effects. Chronic administration of the drug produced only a slight reduction in renal plasma flow, glomerular filtration rate, and in sodium clearance in about half the patients. In 2 patients in which there was little change in the sitting blood pressure cardiac output was unaltered. In a third instance a reduction in cardiac output occurred concomitant with a pronounced fall in sitting blood pressure. Symptoms of left ventricular failure were relieved. Angina pectoris was made worse in 4 of 5 patients and myocardial infarctions were observed while on treatment, but this may have been coincidental. No influence of therapy on the blood clotting mechanism was seen. It was concluded that this drug offers the best present means of controlling the orthostatic blood pressure in severe hypertensive disease.

Maxwell

High-Voltage QRS Complexes in the Absence of Left Ventricular Hypertrophy

By GORDON R. CUMMING, M.D., AND WILLIAM L. PROUDFIT, M.D.

Of an unselected group of otherwise normal electrocardiograms in which the sum of S in V_1 and R in V_5 exceeded 35 mm., 39 per cent came from patients with no clinical evidence of cardiac disease. Of electrocardiograms in which R in aV_L exceeded 11 mm., 29 per cent were from patients without cardiac disease. All of the cases in which the voltage was abnormal in both lead aV_L and the precordial leads had evident or possible heart disease. Thus, while the voltage indexes for left ventricular hypertrophy of Sokolow and Lyon are useful and easy to apply, the lack of specificity of voltage changes limits clinical application.

ELECTROCARDIOGRAMS of patients who have left ventricular hypertrophy frequently demonstrate increased voltage in the left precordial leads.[1] Scott and associates[2] correlated necropsy data from cases of left ventricular hypertrophy with the various electrocardiographic criteria used for diagnosis of the condition, and concluded that those of Sokolow and Lyon[3] were the most inclusive, indicating the abnormality in 80 per cent of cases. The criteria of Sokolow and Lyon differed from those of other authors chiefly with respect to the inclusion of defined voltage limits in the precordial leads. Although the sensitivity of the criteria was satisfactory, the important question of specificity was not investigated. Subsequently Seltzer and associates[4] reported that when 108 electrocardiographic tracings indicative of left ventricular hypertrophy were correlated with the postmortem findings of each case, there were 17 false-positive and 16 questionable results. In 14 of the 17 false-positive findings the voltage index of the precordial leads was abnormal and 12 of the 16 borderline cases had abnormal indices. The results of study of postmortem material may not be strictly applicable to clinical experience for various reasons, but it is evident that false-positive results are common when precordial voltage changes are used as a criterion of left ventricular hypertrophy. Recently Grubschmidt and Sokolow[5] reported that in from 95 to 98 per cent of patients whose electrocardiograms were abnormal only with respect to the RS voltages in various leads there was clinical evidence of left ventricular hypertrophy. Prior to the above publication a similar analysis at the Cleveland Clinic disclosed that as high as 40 per cent of such electrocardiograms come from normal patients. The disparity in findings seems worthy of note.

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METHOD OF SELECTION

One hundred and forty-three electrocardiograms, selected because of voltage changes only, were divided into 3 groups.

Group 1. Electrocardiograms (94) in which the sum of S in lead V_1 plus R in lead V_5 exceeded 35 mm. The records were normal in all other respects, save that in 7 cases the intrinsicoid deflection was inscribed between 0.05 and 0.06 second after the onset of the QRS complex. In none of these cases did the voltage of R on aV_L exceed 11 mm.

Group 2. Electrocardiograms (34) in which the voltage of R in lead aV_L exceeded 11 mm. In no case did the onset of the intrinsicoid deflection exceed 0.05 second, nor did the sum of S and R in leads V_1 and V_5 exceed 35 mm.

Group 3. Electrocardiograms (15) in which the sum of the S in V_1 and the R in V_5 exceeded 35 mm., and the R in aV_L exceeded 11 mm., but which otherwise were normal.

The charts of the 143 patients were reviewed for clinical causes of left ventricular hypertrophy, and the radiologists' reports concerning heart size on 6-foot roentgenograms were noted. These patients were further divided into 3 clinical subgroups.

TABLE 1.—*Correlation of Voltage Value and Clinical Cardiovascular Status, from 143 Electrocardiograms**

Group	Criteria	No. of cases	Clinical cardiovascular status (subgroup) A Normal (%)	B Definite left ventricular hypertrophy (%)	C Possible left ventricular hypertrophy (%)
1	$S V_1+R V_5 > 35$ mm.	94	39	45	16
2	$R_A V_L > 11$ mm.	34	29	53	18
3	$S V_1+R V_5 > 35$ mm. and $R_A V_L >$ mm.	15	0	93	7

*Selected because of voltage changes.

Subgroup A. No clinical evidence of cardiovascular disease.

Subgroup B. Definite clinical evidence of cardiovascular disease or left ventricular hypertrophy.

Subgroup C. Questionable evidence of cardiovascular disease. This group had no evidence for the diagnosis of left ventricular hypertrophy other than transient elevations of blood pressure of not greater than 180/100 mm. Hg. Normal pressures were obtained on 2 subsequent readings without further observations of the hypertension.

All patients were more than 25 years of age; the majority were between 40 and 60 years of age.

RESULTS

Clinical Evidence of Left Ventricular Hypertrophy. These data are given in table 1. In group 1, 39 per cent of patients, in group 2, 29 per cent, and in group 3, no cases, were in subgroup A (showed no clinical evidence of cardiovascular disease). In group 3, 93 per cent of patients were in subgroup B (had definite clinical evidence of left ventricular hypertrophy).

Voltages in Group 1. The ranges and average values for this index are given in table 2. While patients in group 1 had higher voltages than did those in group 2 and 3, there is considerable overlapping. If all voltages under 0 mm. were to be considered normal, then 9 per cent of the electrocardiograms still would come from normal patients and the evidence for left ventricular hypertrophy would be questionable in an additional 6 per cent. At the same time, this extension of the normal range would exclude 25 per cent of subgroup B.

TABLE 2.—*Distribution of Voltage Values in 94 Electrocardiograms, Group 1**

Clinical cardiovascular status (subgroup)	Range of voltage (mm.)	Mean voltage (mm.)	Per cent of total number under 40 mm.
A Normal	36-55	40	55
B Definite left ventricular hypertrophy	36-73	45	25
C Possible left ventricular hypertrophy	36-50	42	40

*Voltage of S V_1 and R V_5.

Voltage of R in V_5 Exceeding 26 mm. In group 1, 44 patients were in this category, 30 per cent of whom were in subgroup A, and 15 per cent in subgroup C. This index, then, is only slightly more selective, and at the same time is absent in many cases in which there is left ventricular hypertrophy.

Roentgenograms. Of group 2, 22 per cent, and of group 3, 60 per cent, had radiologic evidence of left ventricular hypertrophy. All of these cases belonged to subgroup B.

DISCUSSION

There is as yet no large published series of normal values for the precordial leads, so that the frequency distribution of the lead voltage is not known. One possible explanation for the considerable difference in results between the series of Grubschmidt and Sokolow[5] and this series is that the latter was derived from clinic as well as hospital cases, and many patients in the clinic group are normal adults seen for regular periodic examinations. Furthermore, the cases in the report of Grubschmidt and Sokolow were not further divided into subgroups, and more of their patients may have fitted into group 3 of this present series (abnormal voltages in the precordial leads as well as lead aV_L), in which the incidence of clinical left ventricular hypertrophy was very high. Some of the patients of these authors would be placed in the questionable group in this series. Whether patients with transient mild elevations in blood pressure may be said to have left ventricular hypertrophy is highly debatable. It has been observed that the infusion of norepinephrine to

raise the blood pressure from normal to 180/90 mm. Hg, or of epinephrine to raise cardiac rates from about 68 to about 100, may cause an increase in the R and S voltages in leads V_1 and V_5 of up to 20 per cent.[6] Similarly, electrocardiographic voltages might be elevated from normal to "abnormal" by emotional strain.

Cases in which both the precordial and the left arm leads showed increased voltage had a high incidence of clinically evident left ventricular hypertrophy. It would seem that in the presence of left axis deviation the increase of the sum of S in V_1 and R in V_5 to more than 35 mm. is of much greater significance than an electric axis with a value greater than zero.

This lack of exact correlation between RS voltage and left ventricular hypertrophy is not surprising: the position of the electrode is independent of the position of the heart; the thickness of the thoracic wall and the proximity of the heart to the thoracic wall vary; only the outer half of the ventricular wall is said to be responsible for the RS complex;[7] the area under the deflection is more indicative of the forces generated than is the height of the deflection alone; and, finally, it remains to be proved that the electric force increases in proportion to the increase in muscular mass.

Summary

Of an unselected group of "otherwise normal" electrocardiograms in which the sum of S in V_1 and R in V_5 exceeded 35 mm., 39 per cent came from patients with no clinical evidence of cardiac disease. Similarly, 29 per cent of electrocardiograms in which R in aV_L exceeded 11 mm. were from patients without cardiac disease. All of the patients in whom the voltage was abnormal in lead aV_L and the precordial leads had evident or possible heart disease. Thus, while the voltage indexes for left ventricular hypertrophy presented by Sokolow and Lyon[3] are useful and easy to apply, the lack of specificity of voltage changes seriously limits the clinical application.

Summario in Interlingua

In un non-seligite gruppo de "alteremente normal" electrocardiogrammas in que le summa de S in V_1 e R in V_5 excedeva 35 mm, 39 pro cento pertineva a patientes sin evidentia clinic de morbo cardiac. Similemente, 29 pro cento del electrocardiogrammas in que R de aV_L excedeva 11 mm pertineva a patientes sin morbo cardiac. Omne le patientes in qui le voltage esseva anormal in aV_L e in le derivationes precordial esseva subjectos con evidente o possibile morbo cardiac. Assi, ben que le indices de voltage pro hypertrophia sinistroventricular presentate per Sokolow e Lyon[3] es utile e facile a applicar, le manco de specificitate del alterationes de voltage restringe seriemente lor application clinic.

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False "Coronary Patterns" in the Infant Electrocardiogram

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Electrocardiographic patterns of myocardial infarction are rarely found in infancy and suggest, in the first place, an anomalous origin of the left coronary artery. Five infants with such electrocardiograms are reported. In all coronary heart disease could be ruled out, in 4 by autopsy and in 1 by the clinical course. Comparison of these 5 cases with previously reported cases with similar electrocardiograms and autopsy control revealed that coronary patterns in infancy occur in a true and false variety. Some distinguishing features are discussed.

ELECTROCARDIOGRAPHY in infancy is primarily of value in the clarification of abnormal rhythms or in the diagnosis of congenital heart disease by the early detection of hypertrophy or strain of atria and ventricles. Electrocardiographic alterations attributable to functional or organic myocardial derangement have received only scant attention because of the difficulties in distinguishing changes due to primary myocardial disease from normal changes taking place during the first months of life, and the rarity of alterations sufficiently characteristic to suggest specific clinical syndromes. Patterns typical of coronary disease became the subject of special reports,[1-3] particularly when one of the several causes of occlusive coronary disease in infants and children[4, 6] could be ruled out on the basis of autopsy findings.

The fallacy of diagnosing coronary heart disease solely on the basis of "typical" electrocardiographic features is well known for the adult. It can be mimicked by a variety of etiologic factors—degenerative, inflammatory, parasitic, and neoplastic processes—as well as by the effects of drugs, physical agents, emotional states, and even body shape.[6] Disregarding these possibilities, we erroneously diagnosed a congenital anomaly of the coronary blood supply in 2 infants in whom outstanding alterations of the electrocardiogram were the principal available source of information during an acute fulminating fatal disease. In 3 other cases with similar electrocardiographic changes coronary artery disease could be ruled out because of protracted clinical observation and a consideration of circumstances under which these changes developed. The electrocardiographic features of these 5 cases and a comparison of such "false" coronary patterns with true ones documented in the literature are the subject of this report.

Material

Case 1 was a 10-day-old Negro girl who developed cough and dyspnea a few hours before hospitalization. She was in acute respiratory distress with a respiratory rate of 80, a regular pulse of 160, and a temperature of 99.6 F. Except for wheezing over both lungs, the physical findings of the respiratory system were normal. The heart seemed enlarged, but no murmurs were heard. The liver was felt 3 to 4 fingerbreadths below the right costal margin. X-ray revealed cardiomegaly and signs of congestion in both lungs. The hemoglobin was 18.1 Gm. per cent, and the white blood cell count was 10,600, with a normal differential count. The electrocardiogram (fig. 1) showed sinus tachycardia of 140 with a P-R interval of 0.12 second. Prominent Q waves and convex elevated S-T segments merging with small inverted T waves were present in leads II, III, aV_F, V_5, and V_6. Reciprocal QRS and ST-T alterations were found in aV_R and in the right precordial leads. The electrocardiogram was interpreted to represent recent injury with necrosis of the posterolateral wall and apex, and on this basis an abnormal origin of a coronary artery from the pulmonary trunk was suspected. The infant died the next morning.

At autopsy* the heart was markedly enlarged,

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*We are indebted to Dr. O. Saphir for the autopsy data in cases 1, 2, 4, and 5. Cases 1 and 2 were included in a study by Drs. Saphir and N. Cohn on myocarditis in infancy.[7]

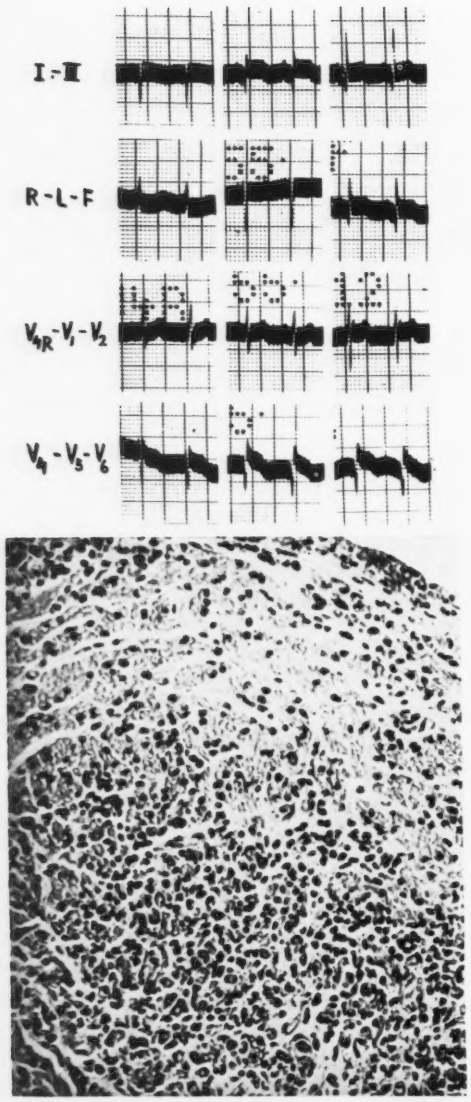


FIG. 1. *Top.* Case 1. Twelve-lead electrocardiogram showing a pattern of recent posterolateral wall infarction. *Bottom.* A section of left ventricle showing the dense cellular infiltrate within necrotic muscle fibers. The endocardium is at the upper right. (Hematoxylin and eosin. × 200.)

particularly to the right. The coronary arteries were normal in origin and distribution. There were a few petechiae on the septal surface of the left ventricle. The myocardium was pale and flabby and there were yellow grayish areas. Microscopic sections (fig. 1) revealed moderate separation of muscle fibers and bundles. In the left ventricle, approximately one third of the myocardial fibers were involved by necrotic alterations. A pleomorphic cellular exudate was scattered throughout the myocardium with increased affinity for the areas of necrosis, and with varying proportions of polymorphonuclear and mononuclear cells. Within the epicardium were aggregates of closely packed mononuclear cells, generally resembling lymphocytes. Inflammatory cells were present in small numbers in the subendocardial connective tissue and there was a small mural thrombus. No inclusion bodies were found. The pathologic diagnosis was acute myocarditis.

Case 2, a 9-month-old white boy had cough and nasal discharge 1 week prior to admission, and developed vomiting, shortness of breath, and progressive stupor before hospitalization. He was lethargic, pale, and apparently in shock. There was flaring of the alae nasi, and the throat was injected. The cardiac rate was 270 and regular. The liver was felt 2 fingerbreadths below the right costal margin. An electrocardiogram (fig. 2) showed a regular supraventricular tachycardia in which P waves could not be definitely identified. The contour of the ventricular complexes was very bizarre, with slurring of QRS in all leads, small Q waves in II and deep Q waves in III and aV_F. The S-T segments were markedly elevated in II, III, aV_F, and V_4 to V_6. Reciprocal S-T depressions were present in aV_R, aV_L, and in V_{4R} to V_2. T waves could not be separated from these S-T deviations. On this basis we suspected an anomalous origin of a coronary artery, causing necrosis of the posterolateral wall, with injury extending to the posterolateral and anterior walls.

The child died 2 hours after admission. Autopsy revealed a heart of normal size with normal origin and distribution of the coronary arteries. The myocardium was flabby and the posterior wall of the left ventricle appeared pale. Microscopically (fig. 2) there was diffuse interstitial infiltration by lymphocytes, mononuclear, and polynuclear cells in varying proportions. A few polymorphonuclear cells were noted in the epicardium. The myocardium showed edema and focal areas of necrosis. Subepicardial areas were more involved than was the subendocardium. No inclusion bodies were found. The pathologic diagnosis was isolated myocarditis.

Case 3, a Negro girl was first admitted to the hospital at the age of 13 months because of severe respiratory distress. Her illness had begun weeks before with symptoms of an upper respiratory infection. Two days prior to admission anorexia, fever, and frequent vomiting were noted. Her past and family histories were noncontributory, her growth and development had been normal and she had no previous illness apart from occa

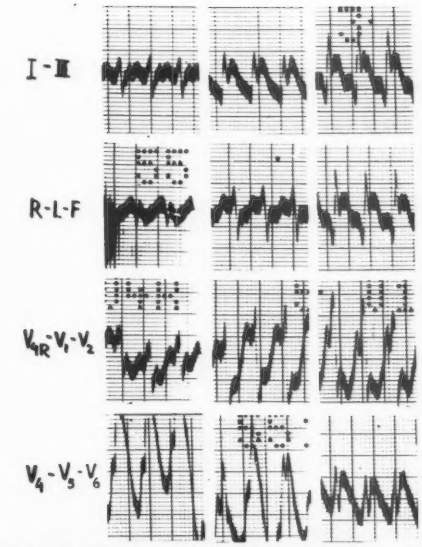
sional upper respiratory infections and atopic eczema. On admission, her temperature was 101.8 F., the pulse rate was 168, the respiratory rate was 63, and the blood pressure was 82 mm. Hg. She had physical findings of right middle lobe pneumonia, and her liver was enlarged to 3 fingers below the costal edge. The heart showed moderate enlargement, a diastolic gallop, and an accentuated second heart sound in the pulmonic area; no murmurs or friction rubs were noted. At x-ray and fluoroscopy, all chambers of the heart appeared enlarged. The pulmonary vascularity was normal. The electrocardiogram (fig. 3, 8-23) showed as the outstanding abnormality an ST-T deviation of discordant type. In leads I, aV_L, and V_4 to V_6, the S-T was markedly elevated in contrast to equally prominent S-T depression in II, III, aV_F, and V_{4R} to V_2. Merging of these displaced S-T segments with T waves resulted in an almost "monophasic" appearance in some leads, pointing to severe acute injury of the anterolateral wall.

The patient was thought to be in congestive heart failure, caused either by myocarditis or, considering the electrocardiographic findings, by an anomalous origin of the left coronary artery from the pulmonary trunk. Studies of etiologic agents included all available viral and bacterial agglutination tests. All were negative, as were other laboratory studies except for acetonuria and a polymorphonuclear leukocytosis (17,100), a 2+ C-reactive protein, and a slightly elevated serum glutamic oxaloacetic acid transaminase on admission. No etiologic agent was established.

She was treated for pneumonitis with antibiotics and was rapidly digitalized, with prompt improvement. The diastolic gallop disappeared as did signs of congestive heart failure, but the heart size remained the same throughout the hospital stay. Serial electrocardiograms revealed a gradual regression of the effects of acute injury with an evolution of symmetrical T inversions (fig. 3, 10-29). Digitalis was discontinued after the pneumonitis had cleared and all evidence of infection had disappeared. A 6-week course with prednisone was instituted in an attempt to accelerate resolution of the myocardial disease, but no changes were observed. When the patient was discharged after 3 months of hospitalization, she was asymptomatic, active, and gaining weight. Cardiomegaly persisted and the electrocardiogram showed slow substitution to an almost normal configuration (fig. 12-24).

At home she did well without medication. Two weeks after discharge, she was readmitted following ingestion of fuel oil. No ill effects were detected.

At 20 months of age she was hospitalized for the third time with symptoms of fever, cough, and anorexia. There was no evident edema, liver enlargement, or respiratory embarrassment at this time. On examination pharyngitis and otitis media were found. A tachycardia with a diastolic gallop was again noted but no friction rub was heard. The initial electrocardiogram on this admission again revealed bizarre changes even more



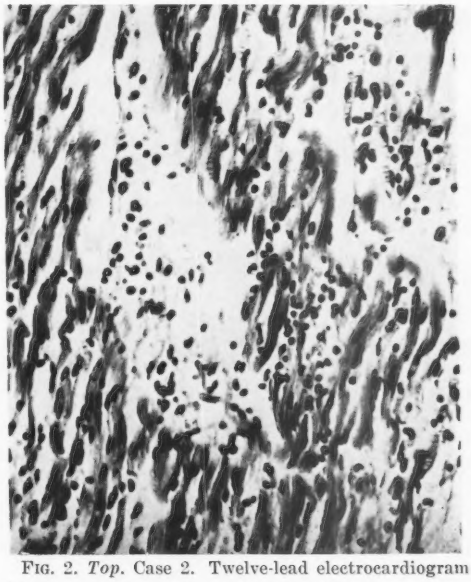


FIG. 2. *Top.* Case 2. Twelve-lead electrocardiogram showing a supraventricular tachycardia and a pattern of recent posterolateral wall infarction. *Bottom.* A section of myocardium showing edema, cellular infiltration, myocytolysis, and early necrosis. (Hematoxylin and eosin. × 200.)

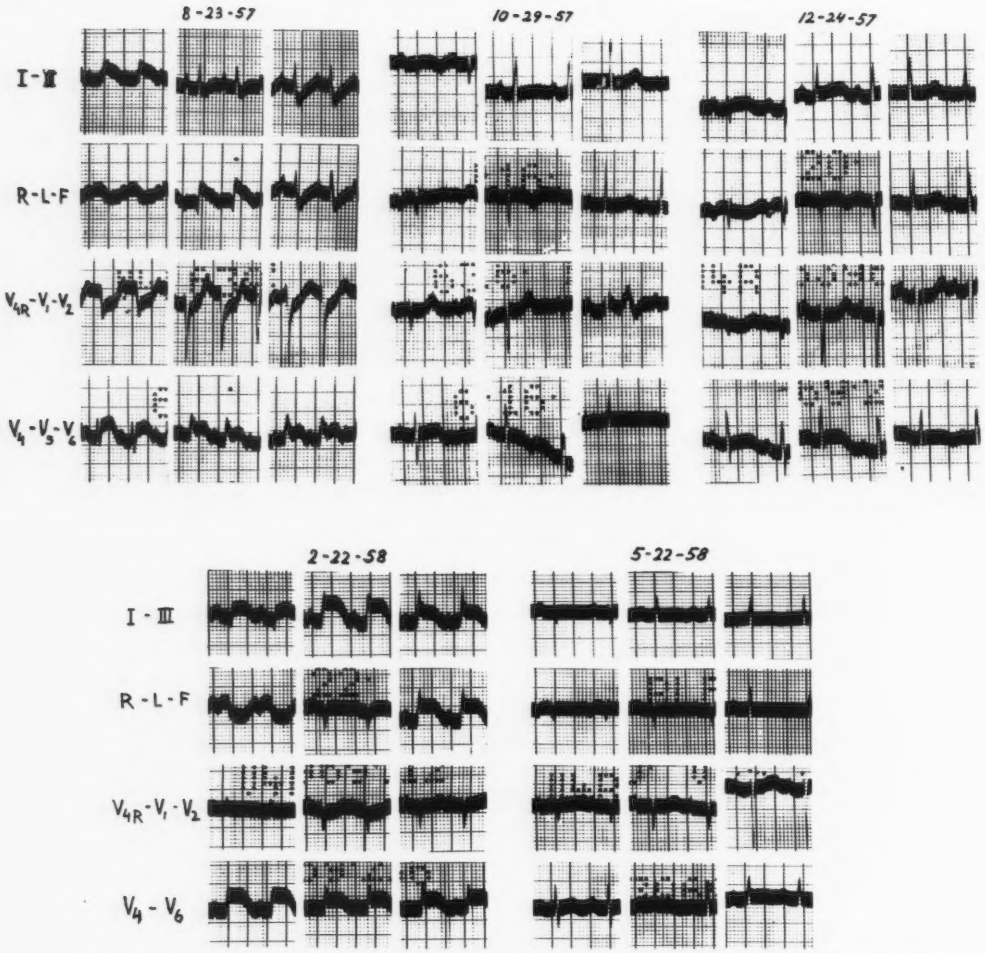
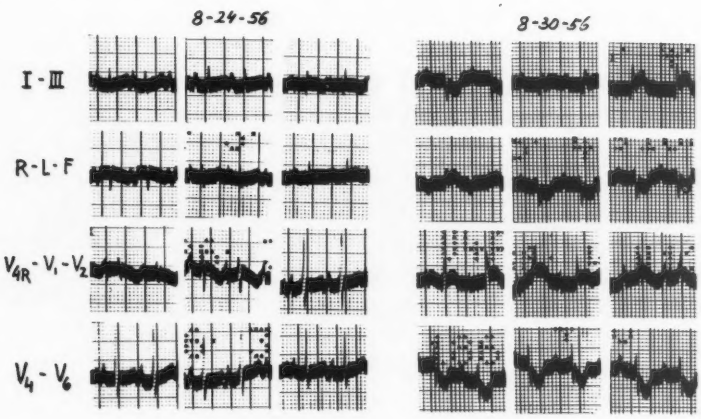


FIG. 3. *Top.* Case 3. Three 12-lead electrocardiograms during the first admission showing recent anterolateral wall injury with restitution. *Bottom.* Two 12-lead electrocardiograms during the third admission showing recent anterior and posterior wall injury with regression to nonspecific abnormalities.

pronounced than previously (fig. 3, 2-22). The S-T elevations were now present in all 3 standard leads and aV_F, while reciprocal S-T depressions were absent in aV_L and over the right precordium, suggesting involvement by renewed severe injury of both anterior and posterior walls. X-ray showed normal lung fields and about the same degree of cardiomegaly as previously observed. The antistreptolysin O titer was elevated (333 units). There was a polymorphonuclear leukocytosis of 14,500 and an elevated transaminase of 56 units. Blood cultures, nose and throat cultures, bacterial and viral agglutinations, urinalysis, and serology revealed no abnormalities. She was treated with antibiotics and digitalis with prompt resolution of the infection, and was discharged after 8 weeks on a maintenance dose of digitoxin.

Again she did well at home until she developed a respiratory infection characterized by fever (105 F.), cough, and abnormal breathing. This occurred 2 weeks after "measles." She was hospitalized for the fourth time and found to have right upper lobe pneumonia, which responded well to the usual methods of therapy. There was no change in the cardiovascular findings. The blood pressure was 90/45 mm. Hg. The heart was en-



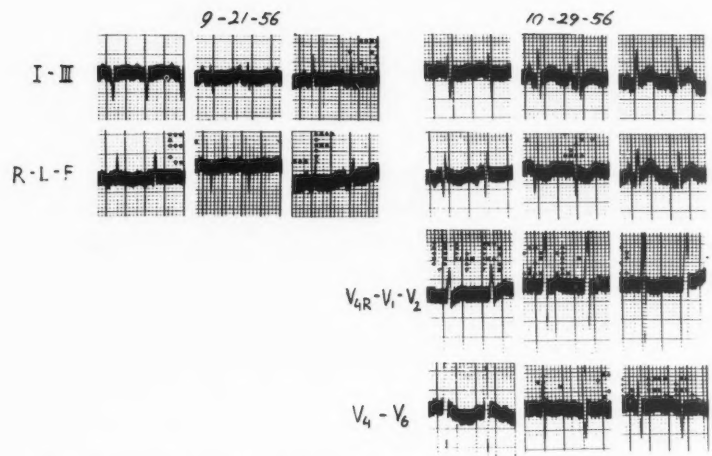


FIG. 4. *Top.* Case 4. Twelve-lead electrocardiograms before and after digitalization.

FIG. 5. *Bottom.* Case 5. Limb-lead electrocardiogram before, and 12-lead electrocardiogram after digitalization.

larged as previously and the electrocardiogram (fig. 3, 5-22) was abnormal with T-wave flattening in all leads, considered to represent a residue of the previous abnormalities. She was discharged after 2 weeks on maintenance digitalis therapy.

The outstanding feature during the observation of the patient in the hospital was her relative well-being at the times that the gallop rhythm and the electrocardiographic abnormalities were most prominent. On the basis of clinical and electrocardiographic findings and the prompt response to digitalis therapy[8, 9] it is believed that she developed acute myocarditis following a respiratory infection at 13 months of age with a recurrence at 20 months of age. The persistence of nonspecific electrocardiographic abnormalities and of the cardiomegaly after several months, suggests chronicity of the myocardial process although the child continued to grow and develop normally and has so far remained without apparent symptoms.

Case 4, a Negro boy, was born at Michael Reese Hospital after 39 weeks' gestation. He seemed normal at birth but was transferred to the pediatric service at 3 days of age because of persistent generalized cyanosis. His pulse rate was 112 per minute and respirations were normal. A grade II harsh systolic murmur was heard at the left sternal edge in the third and fourth intercostal space. A

second heart sound heard in the pulmonic area was of normal intensity and not audibly split. Femoral pulses were easily palpable. Fluoroscopy and x-ray revealed, in the posteroanterior view, a normal-sized heart with lifted apex and concavity in the pulmonary artery segment. The right atrium appeared enlarged and the pulmonary vascularity was decreased. The electrocardiogram (fig. 4, 8-24) showed sinus tachycardia of 158 with a relatively long P-R interval of 0.16 second. The P waves were large, narrow, and pointed in I, II, aV_R, and in V_1 to V_6. In other limb leads they were notched and diphasic. The QRS complexes were tiny in the limb leads with deviation of the QRS axis to the left in the frontal plane. The precordial leads and the T waves of all leads had a normal appearance. These findings were interpreted to represent atrial pathology and, considering the persistent cyanosis, to be compatible with tricuspid atresia.

At 4 weeks of age a severe attack of dyspnea and cyanosis occurred. From 4 to 6 weeks of age similar attacks became increasingly frequent and severe. He was digitalized at 6 weeks of age when he weighed 6 pounds 9 ounces. An unduly large dose (0.5 mg.) of digitoxin was given intramuscularly within a 24-hour period. An electrocardiogram recorded the following day (fig. 4, 8-30) revealed the following changes in comparison with the first: the sinus rate was reduced to 136 and the P-R prolonged to 0.24 second. The QRS complexes were mainly inverted in leads I, aV_L, and aV_F, and predominantly upright in III and aV_R as well as in the right precordial leads. The S-T segment showed a conspicuous discordant displacement, being elevated in II, III, aV_R, and in the right precordial leads, and depressed in all other leads. T waves could not be separated from the S-T segment and the Q-T interval appeared abnormally short (0.20 second instead of 0.26 second $\pm$ 0.05, as expected at this rate.[10] These changes suggesting acute injury involving the diaphragmatic and anterior walls were attributed to unusual digitalis effects, since they were transitory and disappeared in a few days.

An angiocardiogram was taken at 7 weeks of age. It showed that the left heart chambers filled immediately from the right atrium. A left aortic arch was seen to originate from the left ventricle, and a tiny pulmonary artery appeared to communicate with the right ventricle. The impression was of either tricuspid atresia with an atrial and ventricular septal defect or tricuspid stenosis. A surgical attempt to improve pulmonary blood flow by a Potts type of shunt operation was undertaken, but the child died from ventricular fibrillation before surgery was completed.

Autopsy revealed tricuspid stenosis, a thick-walled diminutive right ventricle, and atresia of the pulmonic valve. The foramen ovale and the ductus arteriosus were patent. The right atrium and the left ventricle were dilated and hypertrophic. The coronary arteries originated from a single ostium in the aorta and had a normal distribution. Histologically, the myocardium was slightly edematous and contained large amounts of fibrous tissue.

Case 5, a 10-week-old boy, born after 6½ months of gestation, was doing well until 5 days prior to admission when fast breathing, cyanosis, and slight cough were noted. Examination revealed a respiratory rate of 64 and a regular pulse rate of 140. The thoracic cage showed signs of retraction, and coarse rales were heard over both lungs. There were no murmurs and no signs of congestive heart failure. Chest x-rays showed a heart of normal size and signs of bilateral pneumonitis. An electrocardiogram in which only the limb leads were obtained because of technical difficulties (fig. 5, 9-21) showed sinus tachycardia of 164 with a P-R interval of 0.12 second and no abnormalities in contour.

Signs of congestive heart failure developed a few days after admission. Digitalization was started parentally (0.04 lanatoside C [Cedilanid] intravenously and 0.25 digitoxin intramuscularly) and continued orally in daily doses of 0.105 to 0.030 mg. An electrocardiogram (fig. 5, 10-29) showed an unchanged sinus rate and P-R interval. The precordial leads revealed prominent R waves with an upright T wave in the right precordial leads and predominant S waves in the left, suggesting right ventricular hypertrophy. In the limb leads were conspicuous, discordant S-T deviations—elevation in II, III, and aV_F, and depression in I and aV_L; T waves were not clearly discernible. The Q-T interval appeared foreshortened but when measured in the precordial leads was 0.26 second, well within the normal range.[10] These changes resembling effects of acute injury of the posterior (diaphragmatic) wall, were attributed to unusual digitalis effects, as in case 4. They disappeared in 2 subsequent electrocardiograms.

The patient died after 3 weeks from progressive respiratory insufficiency. Autopsy revealed acute interstitial pneumonia and hemorrhagic bronchopneumonia. There were multiple congenital abnormalities, including a partial anomalous connection of the pulmonary veins to the right atrium, atresia of the upper portion of the vena cava, and entrance of the hepatic vein into the right atrium. The foramen ovale was open. There was hypertrophy of the right ventricle, grossly and microscopically. The coronary arteries were normal in origin and distribution. Sections of the left ventricular myocardium revealed no significant changes.

Discussion

The 5 cases have in common electrocardiographic features of various injury patterns that have been shown[11–15] to follow interference with the function of large areas of ventricular myocardium owing to sudden loss of blood supply or to action of chemical, thermal, or mechanical noxious agents. In all 5, discordant deviations of the S-T segments indicated the presence of injury currents.[13] In cases 1 and 2, in addition, alterations were found in the direction of initial forces of ventricular depolarization, resulting in prominent Q waves in limb and precordial leads. In cases 1 and 3, inversion of T waves was recorded at the time of the S-T deviations or after the disappearance of the latter, indicating a change in the magnitude, direction, and duration of repolarizing forces in some of the affected myocardium. Unless the very unlikely assumption were made that electrogenesis in the infant's heart differs from that in the adult human heart or in the experimental animal, the electrocardiographic features must be explained in the light of present knowledge concerning the genesis of injury effects in general and their manifestations in the scalar electrocardiogram with respect to the location of the exploring electrodes.[14]

In cases 1 and 2, there was an anatomic cause for the pronounced electrocardiographic abnormalities, consisting of a severe inflammatory lesion with diffuse interstitial-cell infiltration and focal necrosis of myocardial fibers, a combination considered by the pathologists to be characteristic of viral myocarditis.[7] Electrocardiographically, the pattern closely resembled, in all aspects, a recent myocardial infarct of the posterior and posterolateral (diaphragmatic) walls of the left ventricle. That diffuse myocarditis in children and adults may imitate in the electrocardiogram a recent myocardial infarct has been shown previously.[1, 17] However, S-T deviations in particular are not a constant feature in this condition.[18–23] In our cases the analogy with a pattern of acute infarct was particularly striking in view of the deep Q waves in the left precordial leads in one, and in leads III and aV_F in the other. Since no confluent area of tissue necrosis was found anatomically, a severe functional alteration of a large portion of the myocardium must have been present, resulting in the failure of the latter to contribute electromotive forces to the initial stages of ventricular activation. The antemortem diagnosis of an abnormal blood supply to the myocardium, on the basis of a congenital anomaly, was disproved by the findings at autopsy of coronary arteries with normal origin and distribution.

On the basis of this experience, the possibility of an acute myocarditis was considered in the interpretation of the bizarre S-T deformations in the first record of case 3 (fig. 3, 8-23). This case bears a striking similarity in clinical and electrocardiographic aspects to a case reported recently[2] and interpreted as myocardial infarction. Both children were older than 1 year and the onset of acute heart failure, cardiomegaly, and electrocardiographic abnormalities followed a respiratory infection. In both, clinical symptoms promptly disappeared after adequate digitalization, but enlargement of the heart persisted and serial electrocardiograms showed an evolution similar to a recent anterolateral wall infarct. Although the latter is the classical electrocardiographic manifestation of an anomalous origin of the left coronary artery, this diagnosis was discarded in our case, and that of an acute myocarditis was preferred, in view of the clinical course and the favorable outcome. Infants ill because of an anomalous origin of the left coronary artery very rarely live beyond 1 year of age and usually die in the third to fifth month,[24] whereas recovery from acute myocarditis is not uncommon, especially in older infants.[7] The assumption of an inflammatory etiology had further support in the recurrence after 4 months of a new episode resembling the first one in clinical and electrocardiographic manifestations. The latter, at this time, were even more conspicuous with involvement of additional leads (II, III, and aV_F). Thus, during reactivation of the presumed inflammatory process, the resulting myocardial lesion appeared more extensive and diffuse, to include the anterolateral as

well as the diaphragmatic aspects of the heart, and became comparable to electrocardiograms recorded in the first 2 cases of proved myocarditis. This concordant type of S-T elevations also raised the question of a complicating acute pericarditis, but this possibility was thought to be excluded on clinical grounds, particularly by the presence of clear heart sounds and the absence of a friction rub and of venous distention. Theoretically, one would not expect that a widespread and scattered lesion of myocarditis would cause S-T deviations.[23] While this is true in the majority of instances,[18–22] currents of injury can be expected to become manifest in the electrocardiogram once a great number of anatomically and functionally compromised myocardial fibers are located close to the epicardium or extend transmurally.

In cases 4 and 5, the discordant S-T deviations resembling acute injury in the diaphragmatic aspects of the heart were attributed to unusual digitalis effects, since their development and disappearance coincided with administration and withdrawal of the drug. At autopsy no anatomic cause was detected to account for these transient electrocardiographic changes. A common coronary ostium in the aorta, present in case 4, does not interfere with normal blood supply to the myocardium.[25] We are aware that electrocardiographic changes of the type illustrated in figures 4 and 5 are at variance with the usual effects of digitalis in adults[26–29] as well as in children and infants.[30–32] Ordinarily the S-T deviations develop in a direction opposite to, rather than parallel to, the main QRS deflection, in keeping with experimentally produced lesions in the subendocardium.[33, 34] However, in some of these experiments, S-T elevations of the type discussed were produced when the animals were exposed to toxic doses of digitalis.[35]

Some of the other changes that developed in case 4, together with the S-T deviations, viz., the prolongation of the P-R interval and the foreshortening of the Q-T, are in keeping with known digitalis effects. More difficult to explain are the alterations in the direction of the QRS complexes that occurred in the limb and right precordial leads in the 2 records of figure 4. A change in the position of the heart appears unlikely, since the P-wave contour remained practically the same in all leads. A better explanation may be that, in this instance, the abnormal electromotive forces responsible for the S-T deviations were "injury currents of activity (demarcation potentials)"[13, 15] rather than "injury currents of rest." The latter are thought to produce S-T deviations primarily by shifting the T-P segment relative to the QRS inscription; the former come into action by virtue of incomplete depolarization of myocardial fibers and thus may result in significant QRS alterations in addition to deviations of the S-T segments.

Our error in diagnosing a congenital anomaly of the coronary circulation in cases 1 and 2 on the basis of electrocardiographic findings prompted us to review similar electrocardiograms reported previously in infants and young children. Considering only cases in whom the cause of abnormalities was established by autopsy, a total of 22 such cases was collected. Fourteen cases had an anomalous origin of the left coronary artery from the pulmonary trunk[36–46] and in all, deep Q waves, S-T elevations, and inverted T waves in various combinations occurred resembling a lesion of the anterolateral wall. In 5 cases[1, 16] an acute myocarditis was established as the cause of the electrocardiographic changes; in 4 of these, the electrocardiographic abnormalities resembled an anterolateral, and in 1 a posterior wall infarct. The remaining 3 cases, all with a pattern of recent anterolateral wall infarction, had various etiologies: In one[9] a primary malignant tumor of the heart was found, in another[5] actual infarction of the left ventricle was due to thrombosis of the left coronary artery, and in the last,[3] a case of complete transposition of the great vessels, necrotic changes in the left ventricle were attributed to acute subsidence of an intracardiac shunt partly compensating for abnormal hemodynamics. Thus, when the 4 autopsy cases of this report are added, the entire material can be divided into 2 almost equal groups consisting of 14 "true"

and 12 "false" coronary patterns. All cases of the former group displayed a pattern of anterolateral wall infarction; in the latter group about two thirds showed a more or less characteristic anterior, and one third a posterior or posterolateral pattern.

The distinction during lifetime between a "true" and a "false" coronary pattern occurring in infants may in the future have important clinical implications. Feasible surgical corrective methods[44] have been developed for abnormally originating left coronary arteries, based on recent studies on the abnormal hemodynamics in this condition and the revision of older concepts of the causes of the associated myocardial ischemia.[25, 47] The electrocardiogram may prove of prime importance when, as in our cases 1 and 2, the observation time is too short to permit a correct diagnosis on clinical grounds and the need for a life-saving procedure is great. The present review would indicate that under such circumstances an anomalous origin of the left coronary artery from the pulmonary artery can be excluded when the electrocardiogram displays features of injury of the diaphragmatic (posterior or posterolateral) aspects of the heart. An anomalous origin of the right coronary artery, which theoretically could produce such changes, is extremely rare and does not give rise to clinically recognizable abnormalities.[25, 48, 49] The finding, on the other hand, of an anterior or anterolateral wall injury pattern does not permit a distinction between a true and a false coronary pattern. Among the several causes of false coronary patterns, an acute myocarditis must be considered first.

Summary and Conclusions

Electrocardiograms are presented of 5 infants with characteristic changes of severe acute injury, imitating patterns of acute myocardial infarction. In 4 of the cases abnormality of the coronary blood supply could be ruled out by autopsy, in 1 it was thought to be excluded on clinical grounds. In 3 the changes were attributable to acute diffuse myocarditis, and in 2 to unusual digitalis effects. A comparison with similar previously reported infant electrocardiograms, in which the etiologic factor could be ascertained by autopsy, suggests that coronary patterns in infancy occur in a "true" and in a "false" variety.

The true variety, caused by a congenital or acquired disorder of coronary blood supply to the myocardium, is associated with a pattern of anterior or anterolateral wall infarction. In the false variety either an anterior or posterior wall pattern may be found. The commonest cause of a false coronary pattern in an infant appears to be an acute diffuse myocarditis.

Acknowledgment

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Summario in Interlingua

Es presentate electrocardiogrammas de 5 infantes, exhibiente le alterationes characteristic de sever injurias acute, simile al configurationes de acute infarcimento myocardial. In 4 del casos, anormalitate del provision coronari de sanguine poteva esser eliminate como causa del alterationes mentionate, gratias al disponibilitate de datos necroptic. In 1, ille explication pareva esser eliminabile super le base de observationes clinic. In 3, le alterationes esseva attribuibile a diffuse myocarditis acute; in 2, a effectos inusual de digitalis.

Un comparation del presente constatationes con simile electrocardiogrammas infantil previemente reportate e permittente le identification de factor etiologic super le base de examines necroptic suggere que configurationes coronari occurre durante le infantia in le 2 varietates de "ver" e "false."

Le varietate ver, causate per congenite o acquirite disordines del provision coronari de sanguine al myocardio, es associate con un configuration de infarcimento de pariete anterior o antero-lateral. In le varietate false, le configuration pote esser illo de infarcimento del pariete anterior o illo de infarcimento del pariete posterior. Le causa le plus commun de un false configuration coronari in infantes pare esser le presentia de diffuse myocarditis acute.

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The test objects were dogs, anesthetized with morphine-nembutal. Quinidine intravenously regularly produce tachycardia in dogs. There was also an immediate hypotension of short duration. The tachycardia was more persistent. Twenty-five minutes after quinidine the cardiac output was not changed significantly. Work of the left ventricle did not change. Systemic arterial resistance was unaltered. However, there was a decrease in right ventricular work and total pulmonary resistance. Moreover, coronary blood flow and cardiac metabolism were markedly increased. Vascular resistance in the coronary bed was diminished. Myocardial efficiency was markedly decreased.

OPPENHEIMER

Biochemical Studies in Full-Blooded Navajo Indians

By REUBEN STRAUS, M.D., JARVEY GILBERT, M.D., AND MOSES WURM, M.S.

The Navajo Indians, who have a low incidence of coronary artery disease and a high fat intake, have also been shown to have significant elevation of serum gamma globulins. In this electrophoretic study of patterns of serum proteins it was found that adult Indians had elevated gamma globulins but that Indian children had electrophoretic patterns similar to white children. These observations indicate that the gamma globulin elevation is not an inherited characteristic in this Indian race and is probably not related to the low frequency of coronary disease.

THE EXTENSIVE studies of Keys and co-workers[1] appear to have established a definitive correlation between the incidence of coronary heart disease with dietary habits and environment of ethnic groups. Sometimes, when these elements fail to account for the manifestation of high or low incidence of coronary artery disease in particular populations, some workers,[2, 3] have drawn upon a hereditary difference as the basis of explanation. This particularly has been the case for the Navajo Indians in whom there has been demonstrated a remarkably low incidence of coronary artery disease, and whose diet, with respect to fat intake, is little different from the normal American population.[4, 5]

It is the purpose of this report to present our findings with regard to the protein composition of the serum of the Navajo Indian.

MATERIAL AND METHODS

A random sample of 25 adult full-blooded male Navajo Indians, ages 25 to 78 years, residing on the Reservation in Fort Defiance, Arizona, was used in this study. The subjects were believed clinically not to have coronary artery disease, and were selected on this basis upon their appearance as outpatients at the local hospital for a variety of minor ailments. Blood was drawn, and immediately after the clot was formed the serum was separated and forwarded to our laboratory, so that the analysis was started within 48 to 72 hours after the specimen was taken.*

A second group of 28 full-blooded Navajo Indian children between the ages of 3 and 15 years, living on the Reservation in Shiprock, New Mexico, were also studied. Blood from these apparently healthy children was secured on a voluntary basis, and specimens were handled in a manner similar to that of the preceding group.

The sera were analyzed by paper electrophoresis, according to the procedure previously described.[6]

RESULTS

Table 1 shows the relative concentration of the 5 major protein components of human serum found in the group of 25 adult males. The mean relative concentration of albumin for this group was 49.0 per cent, which appears not to be significantly different from the normal values obtained in a healthy white population. The mean relative concentration of alpha-1 globulin, alpha-2 globulin, and beta globulin, respectively, are 4.2, 8.8, and 13.1 per cent, all within the range considered normal. The mean relative concentration of gamma globulin of 24.9 per cent, however, is significantly elevated compared to that of a normal white population. With the exception of 3 persons who had normal gamma globulin values, all the remaining specimens ranged higher than the upper limit of normal for a white population.

In order to establish whether or not the elevated gamma globulins observed in these adult Indians represented a genetic or acquired characteristic, a similar analysis in Navajo children was carried out. Table 2 presents the data obtained on relative concentration of protein fractions in the serum

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*The cooperation of Walter Able, M.D., Shiprock, N.M., and Marguerite Kurth, Fort Defiance, Arizona, in securing the serum is gratefully acknowledged.

TABLE 1.—*Relative Concentration of Serum Proteins in Adult Navajo Indians*

Subject	Sex	Age	Albumin (%)	A-1 glob. (%)	A-2 glob. (%)	B glob. (%)	G glob. (%)
T.Y.	M		49.3	5.7	7.3	16.0	21.7
H.K.B.	M	65	56.5	4.1	8.2	11.1	20.1
H.N.	M		49.0	4.9	10.5	11.2	24.5
S.	M	71	46.9	4.7	9.8	12.9	25.8
T.W.	M	48	60.2	3.1	5.8	11.1	19.4
P.C.	M	25	61.0	3.6	6.3	9.7	19.4
W.Y.	M	42	58.8	3.9	8.2	12.2	16.9
M.Y.	M	57	61.1	3.2	5.8	10.6	19.6
B.K.	M	69	49.7	2.0	6.3	12.6	29.5
L.C.	M		53.7	2.5	9.4	11.9	22.4
A.N.	M	71	35.6	6.1	13.5	12.6	32.2
S.S.	M	44	54.2	3.6	5.0	10.3	27.0
E.B.	M	68	54.5	3.7	12.7	14.2	14.9
C.B.	M	66	57.0	4.9	7.7	11.0	19.5
M.	M		39.5	5.0	10.1	11.1	34.3
J.S.	M	50	45.0	3.6	9.6	12.4	29.4
C.J.M.	M	68	32.7	3.9	10.6	17.2	35.6
B.	M	73	47.7	6.1	9.5	7.8	28.8
M.B.	M	45	46.6	6.0	9.1	20.8	17.5
F.J.	M	69	49.4	2.9	8.0	13.3	26.4
P.T.	M	45	48.0	3.8	6.5	15.8	25.9
G.F.	M	62	45.4	3.9	9.1	15.5	26.1
B.S.	M	64	37.2	3.6	7.8	18.2	33.2
J.C.	M	66	42.8	4.6	9.2	15.2	28.2
T.L.	M	68	43.4	5.7	13.4	13.4	24.2
Mean			49.0	4.2	8.8	13.1	24.9
Standard deviation			7.9	1.1	2.3	2.9	5.7
Normal white			50-60	4-8	8-10	12-14	12-18

TABLE 2.—*Relative Concentration of Serum Proteins in Navajo Indian Children*

Subject	Sex	Age	Albumin (%)	A-1 glob. (%)	A-2 glob. (%)	B glob. (%)	G glob. (%)
A.B.	F	7	66.3	4.4	7.8	10.0	11.5
J.B.	F	9	62.5	3.6	7.5	10.1	16.2
R.C.	M	9	63.2	3.4	7.8	9.7	15.9
D.C.	M	11	62.6	3.4	6.8	11.7	15.4
L.L.	M	15	66.8	2.9	7.9	8.6	13.9
D.K.	M	14	61.5	3.5	7.5	9.5	18.0
B.B.	M	13	59.3	4.3	6.8	10.3	19.2
E.R.B.	F	3	55.0	4.3	11.7	13.0	16.0
J.B.	M	11	61.9	4.8	8.6	9.0	15.7
W.L.P.	M	12	65.7	3.7	7.4	8.1	15.1
J.E.	F	11	54.5	3.0	5.9	11.4	25.2
J.H.	M	6	68.0	2.8	8.2	8.9	12.1
T.B.	M	10	63.9	2.3	6.7	8.7	18.4
T.T.	M	12	63.2	3.4	7.5	9.7	16.0
P.R.	M	10	65.8	2.8	4.8	10.5	16.1
M.B.	F	13	64.5	3.5	5.7	11.4	15.0
D.G.	M	11	55.0	3.2	9.5	10.7	21.6
S.B.	M	11	59.8	3.5	9.6	9.8	17.2
W.S.	M	7	54.0	4.4	9.9	10.6	21.1
G.K.	M	4	52.6	3.2	10.0	18.0	16.2
R.B.	F	9	52.7	3.6	6.7	10.4	26.6
A.C.	M	11	59.2	3.5	7.9	11.8	17.6
L.L.	F	6	58.8	3.5	9.3	12.8	15.5
T.Y.	M	10	52.3	3.2	8.3	14.6	21.6
R.H.	F	7	56.8	3.9	8.1	9.1	22.1
M.M.	F	11	55.8	3.3	9.2	10.6	21.1
L.S.	F	6	59.8	3.6	9.6	10.1	16.8
S.Y.	M	11	64.5	3.7	7.4	11.1	13.4
Mean			60.2	3.5	8.0	10.4	17.5
Standard deviation			4.8	.55	1.5	2.1	3.6

of this group. It will be noted that the mean value of most of the fractions is consistently within the range of normal found in a healthy group of white children. White children do not show significant deviations from the range of values for white adults. There are, however, 8 instances of significant increases of gamma globulins. The remaining 20 are within the normal range.

DISCUSSION

Our observations on adult Navajo Indians confirm the previously published data of Paige, Lewis, and Gilbert[5] to the effect that they show an elevated gamma globulin.

The significance of changes in individual protein fractions, as well as the over-all protein pattern, has been well reviewed by Sunderman and Sunderman[7] and Fisher.[8] Our experience during the past 5 years confirms these observations and frequently has enabled us also to make a specific diagnosis based upon characteristic alterations in the protein pattern. Although the child Navajo population as a whole displays a normal relative concentration of all protein fractions, it should be noted that in 8 cases there were moderate increases of gamma globulin. Such changes, particularly within the ranges noted, generally indicate an antibody response to an infectious process, which may be mild, either acute or chronic, and sometimes even subclinical.

Some of the individual protein patterns displayed by the adult population, on the

other hand, are more complex and probably reflect more than a single disease process. For example, R.S. and C.J.M., by virtue of a markedly reduced albumin, elevated beta and gamma globulins, display the protein profile suggestive of liver disease. F.J. and H.K.B., on the other hand, in whom the only major alteration was found to be a marked increase in gamma globulin, possibly reflects repeated infections over a long period of time.

Since the Indian children present electrophoretic protein patterns that resemble a typical white population, it is concluded that a genetic difference does not exist, at least with respect to relative concentration of serum proteins.

It is, therefore, logical to assume that the elevated gamma globulins observed in the adult Navajo are the result of continued exposure to infection or other disease processes rather than of an inherited characteristic. It would be expected that similar gamma globulin levels would be found among people in lower economic groups, or in primitive societies where environment and long-term survival favor frequent infections.

It is our opinion, therefore, that the elevated levels of gamma globulin are not related to the low incidence of coronary artery disease in these people. Keys et al.[9] stated that the diet of the Navajo Indian is not high in total fats and that there are no reliable data on the frequency of coronary sclerosis. On the other hand, one of us,[10] over a 2-year period of resident observation, substantiates both the high level of fat ingestion and the infrequent occurrence of arteriosclerotic heart disease. In this connection a study of the lipid spectra in the Navajo Indian would be profitable.

Whether or not debilitating diseases may operate to reduce the incidence of atherosclerosis, particularly coronary artery disease, as has been reported by Rogers,[10] cannot be determined from the data presented here. Another study correlating coronary artery disease with lipid and lipoprotein findings in tuberculous patients is in progress and will be reported elsewhere.

Summary

Adult full-blooded Navajo Indians sh w significant changes in serum proteins, p r- ticularly elevation of the gamma globuli s.

When protein profiles of full-blooded Na a- jo Indian children are examined, the conc n- tration of the protein fractions is found s- sentially similar to that of a non-Ind n population.

It is concluded that the hypergammaglo n- linemias are not genetically determined t are the result of disease processes.

From our study, there appears to be o relationship between the increase in gam a globulin concentration among adult Nava os and the low incidence of coronary art y disease.

Summario in Interlingua

Adulte indianos navajo de racia pur revela significative idiosyncrasias del proteinas seral. Es specialmente a notar elevationes del globulinas gamma.

Quando le profilos del proteinas de juvenil indianos navajo de racia pur es examinate, le concentration del fractiones de proteina se revela como essentialmente simile a illo del population non-indian.

Es concludite que le hypergammaglobulinemias del indianos navajo adulte non es geneticamente determinate sed representa le resultato de processos pathologic.

Secundo nostre datos, il non pare exister un correlation inter le augmentate concentration de globulina gamma in navajos adulte e lor basse incidentia de morbo de arteria coronari.

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James, A. T. Lovelock, J. E., Webb, J., and Trotter, W. R.: The Fatty Acids of the Blood in Coronary-Artery Disease. Lancet **1**: 705 (Apr. 6), 1957.

These investigators employed a method of gas-liquid chromatography which makes possible the direct isolation, identification, and analysis of all fatty acids between C_6 and C_{20}. The study consisted of an analysis of these fatty acids in 12 coronary artery patients and 12 controls matched as to age and sex and without clinical evidence of coronary artery disease. Red cells, plasma phospholipid, and plasma acetone-soluble fractions were analyzed. The first 2 showed no difference in the proportion of fatty acids between patients and controls. In all 3 fractions the "essential fatty acids," linoleic and arachidonic, were about the same in the 2 groups. In the acetone-soluble fraction of plasma (containing cholesterol esters acid glycerides) there was some suggestion of an increase in the mono-unsaturated C_{14}, C_{16} and C_{18} acids in coronary artery patients compared with the controls. Particularly the ratio of the most abundant of these acids (oleic) to its corresponding saturated acid (stearic) was higher in the patients with coronary artery disease. Since diet seemed to have been identical in the 2 groups, the possibility of a metabolic defect in the coronary artery patients was suggested.

McKusick

Electrocardiographic Response to Exercise in Patients with Mitral Stenosis

By LLOYD H. RAMSEY, M.D., AND JOHN BEEBLE, M.D.

On the assumption that a positive Master 2 step exercise test is good evidence for the existence of myocardial ischemia, the coronary circulation of 40 patients with rheumatic heart disease and isolated mitral stenosis has been tested by this means. The findings in patients of classes I to III are discussed regarding factors that might be responsible and the relationship of the findings to symptomatology in patients with mitral stenosis.

DURING THE PAST several years, clinicians and physiologists alike have devoted considerable attention to the anatomic and physiologic defects proximal to a stenosed mitral valve. The circulatory abnormalities that occur downstream from the obstructed valve and their effects on the over-all functional cardiac reserve of the patient with mitral stenosis have received comparatively little attention.

Hickam and Carghill[1] have demonstrated the inability of the patient with mitral stenosis to increase cardiac output significantly with exercise, in spite of the elevation of pulmonary artery pressure that occurs. Master, Pordy, and Chesky[2] infer that coronary circulation may be impaired by mitral stenosis in their statement that the 2 step exercise test may be useful in determining cardiac function or the status of the coronary circulation in patients with rheumatic heart disease. Yu, Bruce, Lovejoy, and McDowell[3] have reported the effects of exercise on the electrocardiograms of 48 patients with various types of heart disease, which included an undisclosed number of patients with mitral stenosis. Stuckey[4] has demonstrated abnormalities in the postexercise electrocardiograms of patients with mitral stenosis and angina pectoris, but the exercise was severe, being stopped only after the subject developed pain, fatigue, or severe dyspnea. To our knowledge, however, there are no reports of a systematic study of the effects of standardized exercise on the electrocardiogram of patients with rheumatic heart disease and isolated mitral valvular abnormalities.

Based upon the assumption that the changes in the postexercise electrocardiogram that define a positive 2 step exercise test are related to myocardial hypoxia, this study was designed to obtain information concerning the efficiency of the coronary circulation in patients with mitral stenosis who had no associated valvular abnormalities, irrespective of symptoms of chest pain. Patients included in the study had varying degrees of functional cardiac impairment as determined by conventional methods.

METHODS

Changes in the electrocardiogram following exercise have been widely employed as a method for detecting coronary insufficiency in man. The most popular and well standardized exercise test used for this purpose is the Master 2 step exercise test.[5] Master has performed a large number of 2 step exercise tests on normal individuals, making it unnecessary to run large groups of control tests on normal individuals if one adheres to his methods.[2, 5, 6] The results of these control studies allow one to determine, with reasonable certainty, the electrocardiographic changes following exercise that constitute a positive Master test. The test is easily performed, comparatively safe, requires minimal equipment, and the type of exercise is not strange to most patients. For these reasons, the Master single 2 step exercise test was used in this study.

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TABLE 1.—*Results of Master Test in Patients with Mitral Stenosis*

Class	No. of patients	Positive	Negative	Positive (%)
I	5	2	3	40
II	21	16	5	76
III	14	14	0	100
Total	40	32	8	80

Patients were selected at random as they were seen in the hospital and outpatient clinics of the Peter Bent Brigham Hospital and the Vanderbilt University Hospital. A complete history and physical examination was performed on each patient, following which a routine electrocardiogram, cardiac fluoroscopy, and films of the heart were obtained. With this information, the patients were classified as to the severity of their heart disease according to the criteria established by the New York Heart Association.

The presence of a typical murmur of mitral stenosis was considered sufficient evidence for the diagnosis of rheumatic heart disease with mitral stenosis unless other findings raised doubt as to the diagnosis. Patients with multiple valvular lesions were excluded from the study. No attempt was made to determine the degree of mitral insufficiency present or its part in the production of symptoms. Several patients were included in this study who had soft decrescendo diastolic murmurs along the left sternal border in the second to the fourth interspaces. However, these patients had no systolic murmur at the base, a normal pulse pressure, and no evidence of left ventricular enlargement by fluoroscopy or electrocardiogram, and were thought to have relative pulmonary insufficiency and Graham Steell murmurs rather than aortic insufficiency. All patients included in this study had normal sinus rhythm.

Subjects thus selected then performed a single 2 step exercise test at least 2 hours after their last meal. The test was performed as prescribed by Master, and the number of steps climbed during a period of 90 seconds was determined from his published tables.[5] A 12 lead electrocardiogram was taken immediately before exercise. The extremity electrodes were left in place during the exercise by disconnecting the cables at the direct-writing electrocardiograph recorder, and leads CF4, 1, 2, 3 were obtained in that order immediately following the exercise. Five minutes later, a 12 lead electrocardiogram was repeated. Interpretation of the electrocardiograms was made without identification of the patient. Master's criteria were used for determining which tests were positive.

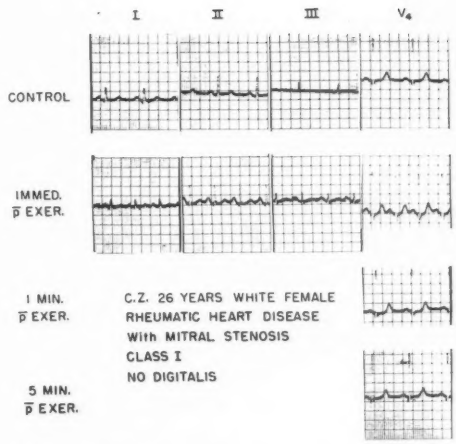

FIG. 1. Positive exercise test. The S-T segment depression is more than 0.5 mm. in lead V_4 immediately after and 1 minute after standard exercise.

RESULTS

Studies have been completed on 40 patients who met the criteria. The subjects' ages ranged from 18 years to 56 years, with a mean age of 33+ years. There were no serious reactions to the exercise although some patients in class III became quite dyspneic following the exercise. Four subjects, all with positive exercise tests, experienced substernal pain with the exercise, which disappeared in less than 5 minutes in each case. Eight patients gave histories of chest pain, anginal in character.

While Master's criteria were used to evaluate the postexercise electrocardiographic changes, isolated directional T wave changes, or atrioventricular and intraventricular conduction defects were not seen in any of the patients tested. With 1 exception the electrocardiographic changes that made the test positive was S-T segment depression of more than 0.5 mm. The exception was a patient who temporarily developed frequent premature ventricular contractions and runs of bigeminal rhythm immediately following exercise.

The results in terms of positive and negative tests are presented for the whole group and each class in table 1.

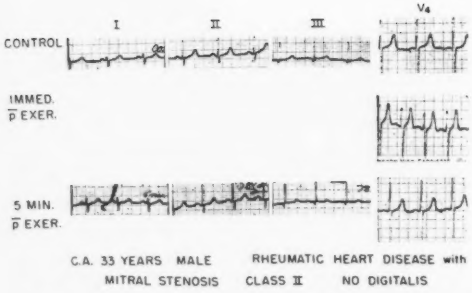

FIG. 2. Negative exercise test. S-T segment is not depressed in spite of a marked increase in pulse rate immediately after exercise.

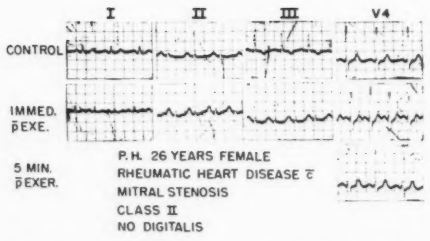

FIG. 3. Positive exercise test. S-T segment depression of more than 0.5 mm. is present in leads II and V_4 immediately after exercise.

Figure 1 shows portions of the electrocardiograms, before and after exercise, of a 26 year old woman who had acute rheumatic fever at age 7 years. She had been known to have a mitral diastolic murmur for 9 years, but was without symptoms and led a normal life.

Figures 2 and 3 show the tracings of 2 other class II patients. While the pulse rate was almost doubled in patient C.A., the postexercise electrocardiogram showed no other changes and the test was interpreted as negative. A similar rate increase in patient P.H. was associated with significant S-T depression.

The tracings in figure 4 are those of a 28 year old woman, class II, who later died during a surgical attempt to relieve mitral stenosis. At autopsy the coronary vessels were completely normal.

DISCUSSION

Apparently a large percentage of patients with mitral stenosis have positive single 2 step exercise tests. This electrocardiographic evidence of myocardial ischemia is present in some patients who are asymptomatic and appear by conventional clinical methods to have little or no impairment of cardiac reserve. This is a particularly striking finding because of the exclusion from the study of patients who revealed any clinical or laboratory evidence of aortic valvular disease.

The possibility must be considered that factors other than coronary insufficiency produced the S-T depression noted following exercise. It is possible that the large number of positive tests resulted in part from the fact that patients were selected from a hospital and outpatient population, and frequently were first seen because of some complaint relating to their heart disease. This selection obviously accounts for the regrettably small number of class I patients. This factor is unimportant, however, when one considers the patients in their clinical class grouping based on history and physical findings. However, the mean age of the group (33 years) would indicate that the patients were, in general, people who had had valvular lesions for some years. This fact is in part counterbalanced by the fact that none of the subjects studied had developed atrial fibrillation, a common later manifestation of mitral stenosis.

It is possible, but unlikely, that hyperventilation per se could be an important factor in the production of electrocardiographic changes in these patients. While the 2 step test does not cause significant hyperpnea in normal subjects, the presence of mitral stenosis makes dyspnea following the test a more prominent feature. However, the changes in the electrocardiogram following voluntary hyperventilation reported by Barker, Shrader and Ronzoni[7] were minor T wave changes and no major S-T depressions were observed. In addition, the vast majority of the subjects in the present study, particularly those in class I and class II, had little or no dyspnea or hyperpnea during or following the exercise

Fourteen of the 40 patients were taking digitalis at the time the exercise test was performed. Yu and his co-workers[8] have reported S-T and T wave changes in the post-exercise electrocardiograms of normal subjects following acute digitalization that were not seen under similar conditions in the same subjects before digitalization. Unfortunately the exercise employed in their study was not comparable to that employed in the 2 step test. Nevertheless, it is quite possible that those subjects taking digitalis have S-T depression at least in part as a result of digitalization. Table 2 shows the results of the Master test in the patients who were not taking digitalis. There is little difference in the percentage of positive tests in the patients not taking digitalis when compared to the whole group.

Recently Myers and Talmers[9] have raised an important question regarding the change in pulse rate that follows exercise and its effect on the T wave of the P wave. These workers consider that frequently the S-T depression seen after exercise can be explained by the change in the amplitude of the P wave and its following T wave. This is believed to result in an elevation of the P-Q segment rather than a depression of the S-T segment. They point out that the contour of the S-T segment is of much more importance than the depression of the S-T segment at its origin. The change in rate following exercise in our patients with mitral stenosis had no constant relationship to significant S-T depressions. However, no attempt was made to define P-Q elevation as a cause of apparent S-T depression, since Master's criteria were used in defining positive tests.

While all the factors discussed above may play at least a minor role in the production of significant changes in the electrocardiogram, from the data available in Master's large experience with the 2 step exercise test, it seems likely that the cause of S-T depression following exercise in the patient with mitral stenosis is coronary insufficiency.

Several events that arise from the mechanical block to blood flow occurring in mitral

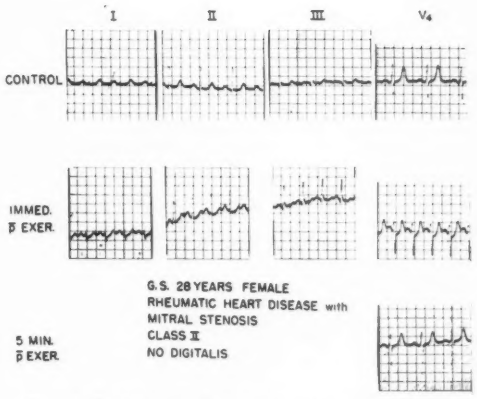

FIG. 4. Positive exercise test. At autopsy the coronary arteries were normal.

stenosis may cause this relative coronary insufficiency. Hickam and Carghill[1] have demonstrated the inability of the patient with mitral stenosis to increase cardiac output with exercise in spite of a concurrent rise in pulmonary artery pressure and increase in heart rate. When the right ventricle works against the increase in pulmonary artery pressure, pressure work increases. This increase in work load results in increased myocardial oxygen consumption, which must primarily be supplied by an increase in coronary blood flow. If this demand for increase in coronary artery perfusion is not met, the result is relative coronary insufficiency.

In the patient with mitral stenosis this demand is made at a time when aortic flow is not increased. Therefore coronary perfusion can be increased only by an increase in arterial perfusion pressure (systemic arterial pressure) or by a decrease in the venous capillary resistance. If the limit of coronary dilatation is reached before or early in exercise and the systemic tissue demands for an increase in blood flow with the exercise prevent an elevation of systemic pressure, the result would be a relative decrease, in relation to need, of coronary perfusion.

Salisbury[10] has been able to demonstrate that failure of the dog's right ventricle in the presence of acute pulmonary hypertension is directly related to the systemic arterial

TABLE 2.—*Results of Master Test in Patients with Mitral Stenosis Not Taking Digitalis*

Class	No. of patients	Positive	Negative	Positive (%)
I	5	2	3	40
II	15	10	5	67
III	6	6	0	100
Total	26	18	8	70

pressure. That is, the dog's right ventricle is capable of withstanding many times the pressure load that usually results in failure when systemic arterial pressure is proportionally elevated. Apparently the increase in coronary artery perfusion pressure accompanying the systemic hypertension results in an augmentation of coronary flow and allows the right ventricle to withstand markedly abnormal strains of pressure work.

In addition to the pressure work factors that may influence the relative coronary perfusion in the patient with mitral stenosis, the increase in heart rate with exercise results in a decrease in the diastolic time component of the cardiac cycle. This also shortens the time available for diastolic perfusion of coronary vessels and could be a further factor in preventing the needed increase in coronary blood flow.

The association of chest pain with mitral stenosis has long been recognized but poorly understood. As Burgess and Ellis[11] pointed out in 1942, there are several types of chest pain in the patient with rheumatic heart disease and mitral stenosis. The psychosomatic type and the pain associated with active rheumatic fever and pancarditis need little discussion. The present studies and those of Stuckey[4] and Salisbury[10] add further evidence that the other 2 categories of pain, angina pectoris and hypercyanotic angina, are caused by a relative coronary insufficiency occurring in an age group not likely to have significant disease of the coronary arteries. It seems probable from the present studies and those of Stuckey that myocardial ischemia does exist in a large percentage of patients with mitral stenosis. The explanation for the variability in occurrence of the symptoms of chest pain and the lack of response of such pain to nitroglycerin and apparent relief with oxygen[12] may well lie in the findings of Salisbury.[10] If systemic arterial pressure bears such a close relationship to cardiac reserve in patients with pulmonary hypertension, it is not difficult to see that the peripheral vasodilatation accompanying the use of nitroglycerin in these patients might well offset the minor coronary artery dilatation expected to occur in normal coronary vessels. Likewise, the lowering of pulmonary artery pressure that may accompany inhalation of 100 per cent oxygen, plus the increase in dissolved oxygen that also accompanies high alveolar oxygen tensions, may actually relieve the myocardial hypoxia by supplying more oxygen per unit blood flow and by decreasing the demand for oxygen by lowering the pressure work load.

SUMMARY

Two step exercise tests performed by 40 patients with rheumatic heart disease and isolated mitral valvular deformities reveal 40 per cent of class I, 76 per cent of class II, and 100 per cent of class III patients to have positive Master tests. It seems unlikely that digitalis, hyperventilation, or rate change with exercise can explain the S-T segment depressions seen on the postexercise electrocardiograms.

It is suggested that myocardial ischemia during exercise in these patients is the cause of the electrocardiographic changes and is a result of the rise in pulmonary artery pressure and the increase in heart rate, which occur in the absence of a significant increase in cardiac output and systemic blood pressure. These factors may well result in a decrease in diastolic perfusion time and effective perfusion pressure of the coronary circulation when the cardiac work load is greatest.

These factors may be important in the production of chest pain in many patients with mitral stenosis and may account for the poor response of the pain to nitroglycerin, since the latter may cause a fall in systemic blood pressure. A resultant decrease in coronary perfusion pressure might well occur if coronary vessels are already maximally dilated.

SUMMARIO IN INTERLINGUA

Tests de exercitio a due scalones, executate per 40 patientes con rheumatic morbo cardiac e isolate deformitates del valvula mitral, revelava resultatos positive secundo Master in 40 pro cento del patientes de classe I, 76 pro cento de class II, e 100 pro cento de classe III. Il es pauco probabile ue digitalis, hyperventilation, o alteration del frequentia como effecto del exercitio pote explicar le depressiones del segmento S-T vidite in le electrocardiogrammas post le exircitio.

Es suggerite que ischemia myocardial durante le exercitio in iste patientes es le causa del alterationes electrocardiographic e que iste ischemia mesme resulta de un augmento del pression pulmono-arterial e del augmento del frequentia cardiac le quales occurre in le absentia de un augmento significative del rendimento cardiac e del pression de sanguine systemic. Iste factores pote ben resultar in un reduction del tempore de perfusion diasfolic e del efficace pression de perfusion in le circulation coronari quando le carga del labor cardiac es le plus grande.

Il es possibile que iste factores es importante in le production de dolores thoracic in multe patientes con stenosis mitral. Illos explica possibilemente le non-satisfacente responsa del dolores al effecto de nitroglycerina, viste que iste agente pote causar un reduction del pression de sanguine in le circulation major. Il es ben possibile que un reduction del pression de perfusion coronari occurre alora si le vasos coronari es jam dilatate maximalmente.

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Time and Concentration Components of Indicator-Dilution Curves Recorded Following Central Injections of Dye in Normal Human Subjects

By STEFAN A. CARTER, M.D., M.Sc., H. J. C. SWAN, M.B., PH.D., AND EARL H. WOOD, M.D., PH.D.

Indicator-dilution curves were recorded by oximeters at the ears and the right radial artery following the injection of Evans blue (T 1824) into the superior vena cava and pulmonary arteries of 37 subjects who had no evidence of cardiovascular disease. The variability and ranges of various time and concentration components of these dilution curves are presented. These values can be used as standards of reference in the interpretation of abnormal dilution curves. Some of the factors responsible for the variability of these values in healthy subjects are assessed and discussed.

THE RECORDING of concentration-time curves at a peripheral arterial site following injection of an indicator into the heart and great vessels provides a valuable tool for the study of normal and abnormal circulation. Its increasing use in diagnostic and research laboratories attests to its efficacy. When this technic is used, it is desirable to have a normal standard of reference with which the values obtained from individual subjects can be compared. The present communication reports the values and the variability of various time and concentration components derived from indicator-dilution curves recorded during catheterization of the right side of the heart in a series of healthy human beings.

METHODS AND SUBJECTS

The right side of the heart was catheterized by the methods previously described,[1, 2] with the subjects resting in the supine position. They had a light meal prior to the study and were given as premedication 30 mg. of codeine sulfate and 100 mg. of secobarbital sodium at the beginning of the procedure. Evans blue (T 1824)* was used as the indicator. Ten milligrams of the dye in 2 ml. of solution was injected into the superior vena cava, main pulmonary artery, right pulmonary artery, or left pulmonary artery. The subjects were breathing 100 per cent oxygen during the recording of the dilution curves, in order to avoid interference due to fluctuations in the oxygen saturation of arterial blood.

Dye-dilution curves were recorded photographically by means of ear oximeters placed on one or both ears and a cuvet oximeter connected to a 20-gage needle in the right radial artery. The sensitivity of the system was such that dye concentrations of 1 mg. per liter gave a deflection of 0.4 to 0.7 cm. for the radial artery curves and 0.2 to 0.8 cm. for the ear oximeter curves.

Time components of the curves recorded by the cuvet oximeter were corrected for the volume of the instrument between the tip of the arterial needle and the middle of the detecting photocell. The time taken for dyed blood to travel from the needle tip in the artery to the detecting element was calculated from the volume of this "dead space" and the flow rate of blood withdrawn through the cuvet system. This time correction was then subtracted from the appropriate time components of the dilution curve. The dead space and physical dimensions of the oximeters were specified in a recent communication.[3] Each milliliter of flow through the oximeter was signaled on the photographic record. The flow rates averaged approximately 23 ml. per minute.

The cardiac output was estimated by the Fick method in 24 subjects while they were breathing 100 per cent oxygen. The average interval between this procedure and the recording of dye-dilution curves after injection into the main pulmonary artery was 7.6 minutes, with a range of 1 to 23 minutes. This interval exceeded 12 minutes in 4 subjects.

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The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

*Supplied through the courtesy of the Warner-Chilcott Laboratories, Morris Plains, N.J.

The concentration and time components of the dilution curves that are the subject matter of this presentation are illustrated in figure 1. Cardiac output, central blood volume, and mean transit time were calculated from the radial artery curves by the Stewart-Hamilton method.[4] In addition the portion of the central blood volume related to the curve proper was calculated from the ratio of the amount of dye injected in milligrams (I) to the peak concentration in milligrams per liter (C_P) as described by Keys and co-workers.[5] This calculation was made only for the curves recorded following injection into the main pulmonary artery. Except for the ratio of least concentration to recirculation concentration obtained from deflections in centimeters, values for concentration components were not measured from the earpiece curves owing to the difficulty of establishing an accurate quantitative relationship between deflection and blood-dye concentration for this instrument.[6, 7]

A group of 37 subjects was studied. It consisted of 17 patients referred to the laboratory to exclude a cardiac lesion as a diagnostic possibility, and 20 healthy physicians. All patients included in this report were considered to have normal cardiovascular systems on the basis of the final evaluation of the clinical and catheterization data. The number of dye curves recorded in these subjects varied from 1 to 4. Intervals between consecutive injections varied from 3 to 57 minutes, with an average of 16 minutes. Only 3 pairs of consecutive curves were separated by more than 30 minutes.

For reasons that will be evident from the results, subjects were divided into subgroups of 23 adult males, 7 adult females, and 7 teen-age subjects (2 females and 5 males). The average ages were 31 (range 26 to 41), 34 (range 22 to 47), and 16 (range 14 to 19) years respectively for the 3 subgroups.

In order to assess the variability of the components of the dye-dilution curves that may occur during the course of the procedure, 5 to 11 consecutive curves recorded in 6 additional resting normal subjects after injection of indicator into the same site (main pulmonary artery or superior vena cava) were analyzed. The interval from the first to the last injection varied from 24 to 60 minutes in these subjects.

Results

Table 1 shows the mean and standard deviation of various time components of the curves recorded at the radial artery following injection into the superior vena cava or pulmonary arteries in 37 subjects who constituted the main experimental group. Considerable variability is evident. The averages of the various time components of the curve obtained after injection into the superior vena cava other than the recirculation time and the least concentration time were all greater than those obtained following injection into the main pulmonary artery or its branches. Paired comparisons revealed that the average differences between the time components of the curves recorded following injection into the superior vena cava and the main pulmonary artery were 1.4, 0.9, 3.8, and 2.8 seconds respectively for the appearance time, build-up time, disappearance time, and mean transit

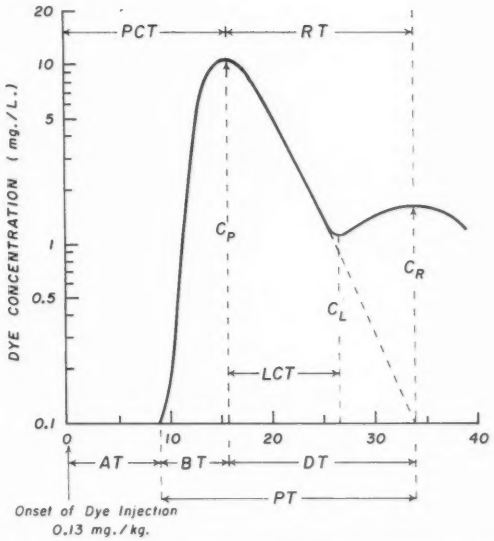

Fig. 1. Time and concentration components of an indicator-dilution curve with extrapolation of the declining slope of concentration, according to the method of Hamilton, to eliminate the estimated effect of recirculated indicator. Time in seconds is represented on the *abscissa* while the logarithm of concentration is shown on the *ordinate*. This dilution curve was recorded for the radial artery following injection of Evans blue into the pulmonary artery of a normal subject.

AT = appearance time, BT = build-up time, C_L = least concentration, C_P = peak concentration, C_R = recirculation concentration, DT = disappearance time, LCT = least concentration time, PCT = peak concentration time, PT = passage time, RT = recirculation time.

TABLE 1.—*Averages and Variability of Time Components of Dye-Dilution Curves Recorded at the Radial Artery in Normal Subjects**

Subgroup	Subjects	Site of injection	Time components (seconds) AT Mean	AT S.D.	BT Mean	BT S.D.	PCT Mean	PCT S.D.	DT Mean	DT S.D.	PT Mean	PT S.D.	MTT Mean	MTT S.D.	LCT Mean	LCT S.D.	RT Mean	RT S.D.
	11	RPA	10.9	1.8	6.1	0.9	17.0	2.5	19.8	4.2	25.9	5.0	19.1	2.9	13.1	2.5	21.8	2.7
Adult male	11	LPA	10.0	2.3	5.8	1.0	15.8	3.0	17.1	4.3	22.9	4.9	17.7	3.9	12.1	2.5	20.2	2.1
	16	MPA	11.7	2.2	6.1	1.0	17.8	3.0	20.3	4.4	26.4	5.2	19.5	3.3	12.8	2.3	21.4	3.4
	9	SVC	13.2	3.0	7.0	0.9	20.4	3.5	23.8	4.6	30.8	5.1	22.7	4.3	12.6	1.5	21.5	1.9
Adult female	5	MPA	7.0†	1.6	4.8†	0.6	11.9†	2.1	14.8‡	2.3	19.6‡	2.7	13.1†	2.1	9.7‡	1.1	16.1†	1.7
	6	SVC	8.4†	1.8	5.3†	1.0	13.7†	2.5	16.8†	3.2	22.0†	4.0	15.0†	2.6	9.9†	1.2	17.0†	1.5
Teen-age	6	MPA	7.5†	1.3	4.8‡	0.9	12.3†	1.9	15.0‡	1.7	19.9‡	2.6	13.5†	1.8	9.0†	1.0	16.2†	2.3
	7	SVC	9.3†	1.5	5.9‡	1.1	15.2†	2.2	19.1	4.4	25.0	5.3	16.9†	2.6	10.3‡	2.1	17.3†	2.8

*Abbreviations: AT = appearance time, BT = build-up time, PCT = peak concentration time, DT = disappearance time, PT = passage time, MTT = mean transit time, LCT = least concentration time, RT = recirculation time, RPA = right pulmonary artery, LPA = left pulmonary artery, MPA = main pulmonary artery, SVC = superior vena cava, and S.D. = standard deviation.

†$p < 0.01$ for difference from male subgroup.

‡$p < 0.05$ for difference from male subgroup.

time. The p values for all these differences were less than 0.01.

Considerable variability of the time components following injection at any one site is also evident in table 1. An attempt was made to relate this variability to differences in cardiac output, blood volume, and body size encountered in these subjects. Figure 2 shows the relationship of the appearance time, build-up time, and recirculation time from the curves recorded at the radial artery after injection into the main pulmonary artery to the cardiac output as estimated by the Fick method, the part of the central blood volume related to the curve proper (I/C_P), and the surface area. The appearance time increased with the blood volume (I/C_P) and the surface area, but showed no correlation with cardiac output. Build-up time and recirculation time, on the other hand, correlated with cardiac output, and build-up time also correlated well with surface area. Build-up time and recirculation time also correlated well with cardiac index ($p < 0.01$), whereas no definite correlation of appearance time with cardiac index could be demonstrated. Most of the time components were significantly shorter in the adult female and teen-age subgroups than in the adult male subgroup. However, the surface area was significantly larger in the adult males than in the adult females and the teen-age subjects. Correction of the appearance time, build-up time, and recirculation time for the surface area by dividing these time components in seconds by the surface area in square meters eliminated the correlation with surface area. However, the average values for the corrected appearance time and recirculation time, but not for the build-up time, were significantly greater in the adult male subgroup than in the other 2 subgroups. The over-all average values for the corrected time components were 5.4, 3.1, and 10.5 seconds per square meter for the appearance time, build-up time and recirculation time, and the standard deviations of these values were 1.4, 0.5, and 1.9 seconds per square meter respectively.

The data on cardiac index, central blood volume, disappearance slope, and various concentration components of the same curves are shown in table 2. Paired comparisons revealed that the central blood volume, the least concentration, and the ratio of the least concentration to the recirculation concentration were significantly larger, whereas the peak

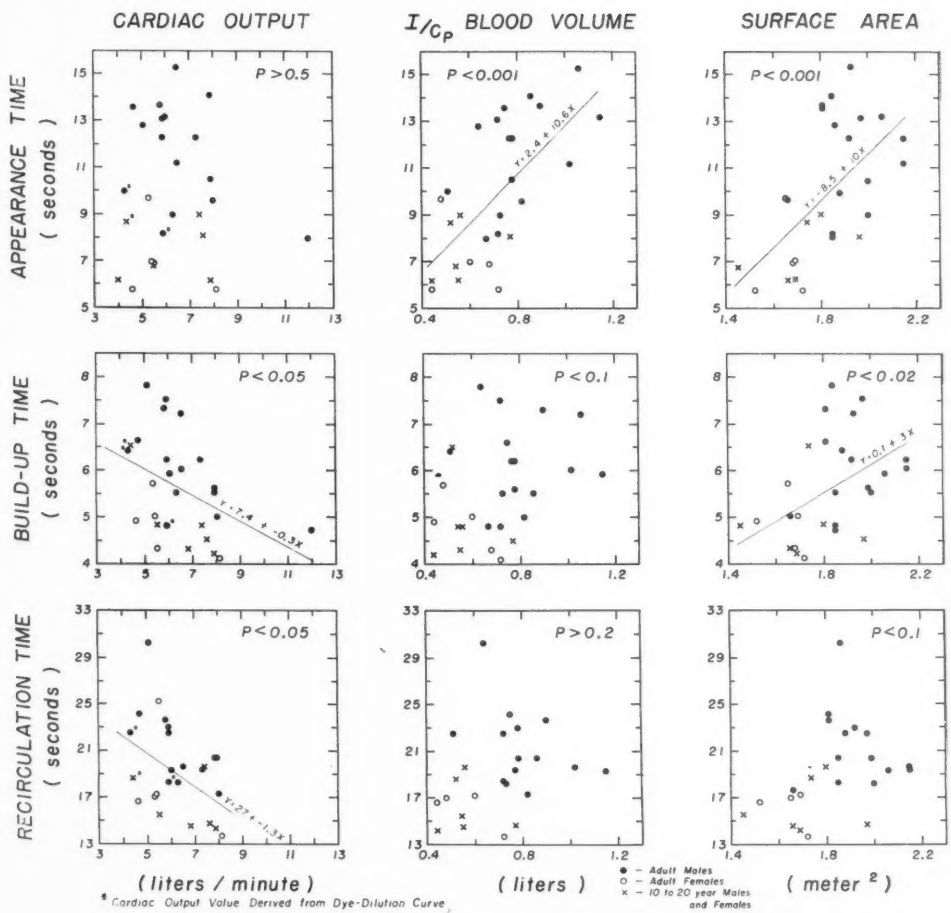

FIG. 2. Relationship of the appearance, build-up and recirculation times to the cardiac output (estimated by the Fick method) blood volume (I/C_P) and surface area for dilution curves recorded at the radial artery following the injection into the main pulmonary artery of healthy persons. *p* values of the regression coefficient are given at the *top* of each panel. Note: 1. Correlation of the appearance time with the blood volume (I/C_P) and the surface area and absence of correlation with cardiac output. 2. Correlation of the build-up and recirculation times with the cardiac output and of the build-up time with the surface area.

oncentration and the disappearance slope vere significantly smaller in the curves obained after injection into the superior vena ava than after injection into the main pulnonary artery. On the other hand, paired omparisons of cardiac index calculated from he dye curves from various sites did not show any systematic differences. The differences in the various components shown in table 2 among the 3 subgroups of subjects did not attain statistical significance, except for the difference in the disappearance slope of the curves recorded after injections into the superior vena cava in the male subgroup as compared with the female subgroup, which might be related, at least in part, to the higher mean cardiac index in the latter subgroup.

The values for various time components and the ratio of the least concentration to the recirculation concentration for the curves re-

TABLE 2.—*Averages and Variability of Concentration Components and of Other Parameters Derived from Dye-Dilution Curves Recorded at the Radial Artery in Normal Subjects**

Subgroup	Subjects	Site of injection	Cardiac index (L./min./M.²) Mean	S.D.	Central blood volume (ml./Kg.) Mean	S.D.	Disappearance slope† Mean	S.D.	Concentration (mg./L./mg./Kg.) C_P Mean	S.D.	C_L Mean	S.D.	C_R Mean	S.D.	C_L/C_R Mean	S.D.
Adult male	11	RPA	3.0	0.6	24.9	4.7	0.289	0.094	99.0	18.7	7.0	1.6	18.8	4.4	0.42	0.12
	11	LPA	3.4	0.9	24.9	4.5	0.323	0.105	97.1	22.5	6.0	2.6	16.7	3.8	0.36	0.14
	16	MPA	3.3	0.8	27.0	7.0	0.301	0.091	95.7	21.4	6.8	2.6	16.7	3.7	0.40	0.09
	9	SVC	3.1	0.6	29.0	8.4	0.242	0.053	89.3	28.8	9.4	2.6	17.9	2.3	0.56	0.14
Adult female	5	MPA	3.4	0.9	22.9	3.9	0.365	0.047	103.1	17.1	7.9	1.9	18.4	2.6	0.42	0.06
	6	SVC	3.8	0.9	25.5	4.6	0.349‡	0.083	98.3	18.9	9.0	2.2	19.4	5.3	0.47	0.16
Teenage	6	MPA	3.5	0.6	21.7	3.9	0.384	0.057	112.7	21.0	8.7	2.9	18.8	7.2	0.47	0.08
	7	SVC	3.4	0.8	26.0	4.5	0.310	0.142	97.2	18.5	9.7	5.1	17.1	6.2	0.55	0.14

*Abbreviations: C_P = peak concentration, C_L = least concentration, C_R = recirculation concentration, and S.D. = standard deviation. Other abbreviations as in table 1.

†Disappearance slope $= \frac{\log_e C_1 - \log_e C_2}{t_1 - t_2}$ where C_1 and C_2 are 2 concentrations chosen at random on the disappearance slope before the occurrence of recirculation, and t_1 and t_2 the corresponding times in seconds.

‡$p < 0.01$ for difference from male subgroup.

corded at the left ear are presented in table 3. The differences between subgroups and injection sites were similar to those obtained from radial artery curves.

The appearance time was longer in the curves recorded from the radial artery than those recorded at the ear, while no significant systematic difference was evident in the other time components. Furthermore, as illustrated in figure 3, the difference between the appearance times of the curves recorded at the radial artery and at the ear increased with the absolute value of the appearance time.

Comparison of the time components recorded at the right and left ears showed no systematic differences. The mean differences did not exceed 0.1 second.

The variability, with time, of repeated determinations of appearance time, build-up time and recirculation time of the dye-dilution curves recorded at the left ear and right radial artery following successive injections into the same site in 6 subjects is illustrated in figure 4. In some subjects these components showed no systematic change with time while in others there was some progressive prolongation or shortening during the period of observation. However, the appearance time and build-up time remained relatively stable and usually did not vary by more than 2 seconds, whereas the recirculation time frequently showed wider variation.

DISCUSSION

The variability of such parameters as those that form the basis of the present study can be due to technical or biologic factors. Technical factors involved in the recording and analysis of dye-dilution curves include potential errors in the measurement of records or signaling of the exact moment of dye injection, correction for the "dead space" of the cuvet-oximeter system between the artery and photocell, calibration of the instruments in terms of dye concentration, possible differences in dynamic response among various oximeters used, and variation in the same instrument with time. These factors ordinarily could account for only a small part of the variability that has been demonstrated and that can be exemplified by a range of 5.8 to 15.3 seconds in the case of appearance time recorded at the radial artery following the injection of dye into the main pulmonary artery.

The greatest part of this variability is most likely due to the biologic intra-individual and interindividual differences. Many components of indicator-dilution curves vary in the same

TABLE 3.—*Averages and Variability of Time Components and of the Ratio of Least Concentration to Recirculation Concentration in Centimeters Deflection, from Dye-Dilution Curves Recorded at the Left Ear in Normal Subjects**

Sub-roup	Subjects	Site of injection	Time components (seconds) AT Mean	AT S.D.	BT Mean	BT S.D.	PCT Mean	PCT S.D.	RT Mean	RT S.D.	C_L/C_R Mean	C_L/C_R S.D.
dult	16	MPA	7.6	1.2	6.0	0.9	13.6	1.8	21.5	3.5	0.34	0.11
ale	9	SVC	9.1	1.5	6.5	0.6	15.8	2.0	21.0	1.6	0.44	0.17
dult fe-	5	MPA	5.9†	0.8	5.0‡	0.7	10.9†	1.4	16.4‡	1.8	0.46	0.06
ale	6	SVC	7.4‡	1.0	5.4†	0.9	12.8†	1.6	17.0†	0.6	0.45	0.04
een-	6	MPA	6.2‡	1.1	5.2	1.0	11.4‡	2.1	16.4†	5.2	0.53	0.17
ge	7	SVC	8.1	1.5	6.4	0.9	14.5	2.3	18.0	2.8	0.61	0.09

*Abbreviations the same as in tables 1 and 2.
†$p < 0.01$ for difference from male subgroup.
‡$p < 0.05$ for difference from male subgroup.

ndividual when the injection sites or sampling sites are changed. Differences observed in the present study between the components of dilution curves recorded after injection into the superior vena cava and those recorded after injection into the main pulmonary artery and its branches confirm the observations of Hetzel, Swan, and Wood,[8] who found that as the injection site was moved peripherally, the time components other than the recirculation time were prolonged, peak concentration was reduced, and central blood volume was increased. However, their report was based mainly on a group of patients with cardiac abnormalities. The present study, which is based on subjects without cardiac disease, demonstrates in addition that the least concentration time was also independent of the injection site, similar to the finding in respect to recirculation time. These authors ascribed their findings to the longer anatomic path between injection and sampling sites which is traversed by the dye and to increased longitudinal dispersion of the dye as it passes from the more peripheral to the central injection site. Similarly, appearance times in curves recorded at the radial artery that were longer than those recorded at the ear probably reflect the longer anatomic pathways to the radial sampling site. The finding that this difference increased with the absolute value for the appearance time is consistent with this explanation. The absence of systematic differences in the value for cardiac output obtained by the dilution technic following injection of indicator into the various sites, which was also reported by Hetzel and co-workers,[8] allows estimation of cardiac output from dye-dilution curves recorded after injection at these various sites.

When the injection sites and the sampling sites are the same, intra-individual variations apparently still occur probably because of changes in the hemodynamic status of the subject. The present study showed that the appearance time and build-up time changed relatively little and were more stable than the recirculation time in a series of repeated dye-dilution curves. Small intra-individual variability of various circulation times[9, 10] and more recently of the appearance time and the peak concentration time[11] has been reported previously. These considerations are important with respect to the validity of comparing components of dye-dilution curves recorded successively following injection into different sites. Such comparisons may be of practical importance; for example, comparison of appearance times following injection into the venae cavae, branches of the pulmonary artery and pulmonary veins is of value in the diagnosis of anomalous pulmonary venous drainage.[12] In adult and teen-age patients differences in the appearance time of less than

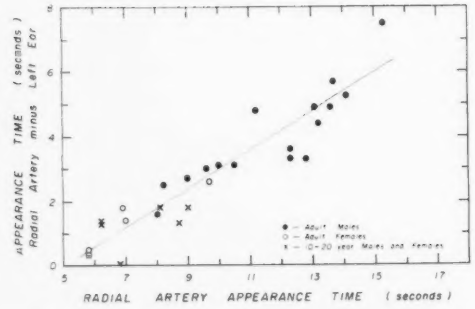

FIG. 3. Relationship of the difference between the appearance times from curves recorded at the right radial artery and the left ear to the actual value for the appearance time at the radial artery. Data obtained from curves recorded after the injection into the main pulmonary artery of healthy persons. Note the rather close positive correlation between the fastest circulation time from the pulmonary to the radial artery (i.e., the appearance time) and the difference between the fastest circulation times to the ear and the radial artery at the wrist. The symbols are the same as those used in figure 2.

2 seconds between any two curves may not be significant. Care must be exercised in comparing time components of curves recorded at longer time intervals, such as 30 or 40 minutes, in view of the tendency exhibited by some subjects to progressive prolongation or shortening of the time components with time.

Assessment of interindividual variation reveals lack of definite correlation of the appearance time with cardiac output, but good correlation with surface area and blood volume (I/C_P). Direct comparison with the "central blood volume" was not carried out because the values for appearance time and also build-up time are included in the calculation of "central blood volume." The blood volume (I/C_P) that was correlated with the time components is calculated independently of any measurement of time components of the dilution curve and is a measure of the dispersion of the injected indicator during its passage from the injection site to the sampling site.[5] Dispersion of the indicator in turn is thought to be dependent in part upon the volume of blood between the injection site and the sampling site. Good correlation of appearance time with blood volume (I/C_P) and surface area, which is in turn correlated with total blood volume of the subject, suggests strongly that a large part of the interindividual variability for appearance time is due to the differences in central blood volume.

A good negative correlation of build-up time and recirculation time with cardiac output is probably due to the lesser dispersion of the indicator in subjects with high rates of flow. Furthermore, in subjects with the same total blood volume an inverse relationship between cardiac output and the time required for dyed blood to make a complete circuit of the vascular system (systemic recirculation time) would be expected. Positive correlation of build-up time with surface area could be explained again by greater dispersion of the indicator in subjects with greater blood volume, as indicated by greater surface area. Lack of correlation of build-up time and recirculation time with blood volume (I/C_P) is difficult to explain. Metabolic rate and heart rate are known to be related to the velocity of the circulation,[13] and undoubtedly several unexplored parameters of the circulation and body size in addition to those that have been discussed enter into the determination of interindividual variability. Because of the good correlation of appearance time and build-up time with surface area and a trend in that direction in the case of recirculation time, the expression of various circulation times as circulation "indexes" in seconds per square meter may allow a more valid comparison of the time components of the indicator-dilution curves in various patients.

All the time components in the adult males were longer than those in the adult females and the teen-age subgroup (mainly male). Blumgart and Weiss[9] previously reported short circulation times in teen-age subjects and Dees and co-workers[11] found shorter circulation times in females than in males. However, the body size of our male subgroup was significantly greater than in the other two subgroups, which probably accounts, at least in part, for the longer time components in the adult males. Correction for body size by dividing the appearance time, build-up time

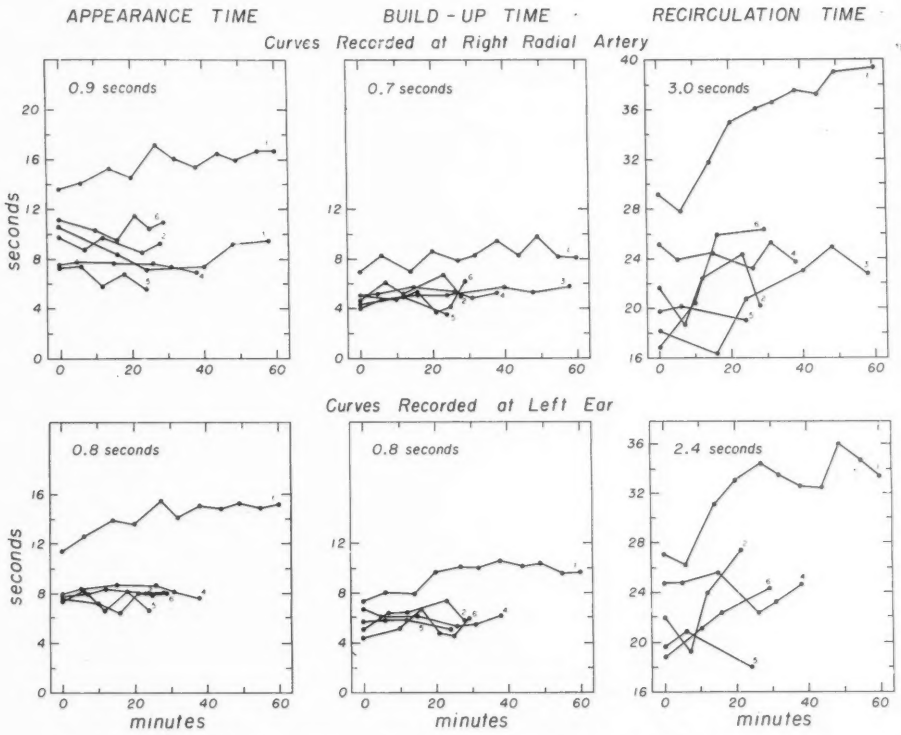

FIG. 4. Intra-individual variability in appearance, build-up and recirculation times of dilution curves recorded at the radial artery and ear of 6 persons following repeated injections of the indicator into the same site on the right side of the heart. Numbers identify time components of each person in various panels. Variability expressed as the square root of the average variance of all persons is indicated at the top of each panel in seconds. Note relatively small changes of the appearance and build-up times and wider variations of the recirculation times.

and recirculation time by the surface area did not abolish significant differences in the appearance time and recirculation time between the male subgroup and the other 2 subgroups. This means either that factors other than differences in body size are responsible for part of the observed difference or that the correction for body size on the basis of surface area was not complete. Dees and co-workers[11] found, further, that the time components were longer in the subjects more than 40 years of age. Only a few subjects were in this older group in the present study. However, no systematic difference could be demonstrated between males more than 30 years of age and those less than 30 years of age.

Although considerable variability of various components of indicator-dilution curves exists in normal subjects, gross changes occur in conditions such as congestive heart failure, thyrotoxicosis, and others,[13, 14] and result in components outside the range encountered in normal man. Deviations from normal are particularly evident and of practical importance in patients with congenital heart defects or valvular heart disease.[15] Values that exceed 2 times the standard deviation from the mean as set forth in the present study should be considered abnormal.

A special consideration has been given to the ratio of the least concentration to the recirculation concentration of the curves re-

corded at the radial artery, since it has been shown to be increased in patients with predominant valvular regurgitation[16] and in those with left-to-right shunt.[17] All the values recorded in the present group of normal subjects were less than 0.60 for the curves recorded after injection into the pulmonary artery and less than 0.85 after injection into the superior vena cava. The finding of larger values should therefore arouse suspicion that one of these lesions exists. Curves recorded by ear oximeters appear to be less reliable for this purpose.[16]

Summary

Indicator-dilution curves were recorded by oximeters at the radial artery and at the ears, following injection of Evans blue (T-1824) into the superior vena cava and the pulmonary arteries of 37 subjects who had no evidence of cardiovascular disease.

The variability and range of various components of these curves are reported. Curves recorded following injection into the superior vena cava showed significantly longer time components, other than the recirculation time and the least concentration time, than the curves recorded following injection into the main pulmonary artery. Also, the "central blood volume," the least concentration, and the ratio of the least concentration to the recirculation concentration were larger, whereas the peak concentration and the disappearance slope were smaller in the curves recorded after injection into the superior vena cava. The values for cardiac output calculated from the curves following injection into the superior vena cava showed no systematic difference from those following injection into the pulmonary arteries.

The appearance time was significantly shorter in the curves recorded at the ears than in the curves recorded at the radial artery, whereas other time components showed no systematic difference.

The time components of the curves recorded at the right and left ears were practically identical.

The appearance time and the build-up time remained relatively stable when injection of the indicator into the same site in the same subject was repeated several times over a period of 30 to 60 minutes, whereas the recirculation time showed wider variations.

Significantly longer time components of the curves recorded in the adult males as compared to the adult females and teen-age subjects are thought to be related chiefly to the larger body size of the adult males.

Rather large interindividual variability of various components of indicator-dilution curves recorded in normal subjects could be accounted for in large part by the differences in body size, blood volume, and cardiac output.

Acknowledgment

This study was made possible by the unstinting cooperation of many professional and technical colleagues. The authors are particularly indebted to Miss M. Koelsch, Mrs. J. Frank, Miss L. Cronin, and Mr. W. F. Sutterer for their help and interest in this study.

Summario in Interlingua

Curvas del dilution de colorante indicatori esseva registrate per oxymetros al arteria radial e al aures post le injection de blau de Evans (T-1824) in le vena cave superior e le arterias pulmonar de 37 subjectos qui exhibiva nulle signo de morbo cardiovascular.

Le variabilitate de diverse componentes de iste curvas es reportate. Curvas registrate post injectiones in le vena cave superior exhibiva significativemente plus longe componentes temporal—a parte le tempore de recirculation e le tempore del concentration minimal—que le curvas registrate post injectiones in le principal arteria pulmonar. In plus, le "volumine de sanguine central," le concentration minimal, e le proportion inter le concentration minimal e le concentration de recirculation esseva plus grande, durante que le concentration maximal e le inclino de disparition esseva plus miere in le curvas registrate post injection in le vena cave superior. Le valores del rendimento cardiac, calculate ab le curvas post injectiones in le vena cave superior, non differeva systematicamente ab le valores calculate post injectiones in le arteria pulmonar.

Le tempore de apparition esseva significativemente plus breve in le curvas registrate al aures que in le curvas registrate al arteria radial, durante que le altere componentes temporal non differeva systematicamente.

Le componentes temporal del curvas registrate al aure dextere e al aure sinistre esseva practicamente identic.

Le tempore del apparition e le tempore de accumulation remaneva relativemente stabile quando le injection del indicator in le mesme sito in le mesme subjecto esseva repetite plure vices intra un periodo de 30 a 60 minutas. Le tempore del recirculation monstrava plus grande variationes.

Le constatation de significativemente plus longe componentes temporal del curvas registrate in masculos adulte in comparation con le constatationes in adulte femininas e in adolescentes es interpretate como primarimente un effecto del plus grande dimensiones corporee in masculos adulte.

Un satis grande variabilitate interindividual de varie componentes del curvas del dilution de colorante indicatori in subjectos normal esseva explicabile in grande parte per differentias del dimensiones corporee, del volumine de sanguine, e del rendimento cardiac.

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CLINICAL PROGRESS

Staphylococcal Bacteremia and Endocarditis

By RICHARD H. MEADE, III, M.D.

STAPHYLOCOCCAL bacteremia with or without endocarditis is as great a threat to life today as it was before specific antibacterial treatment was available. The numerous instances in which cures have been effected by the administration of one or more of the potent antibiotic drugs do not belie this statement. Soon after penicillin and other effective antistaphylococcal drugs were put into general use, there was a dip in mortality statistics which seemed an encouraging harbinger of the expected trend. Since 1948, however, the death rate has in most clinics approached that which existed before the antibiotic era. This apparent failure of current therapy to reduce mortality appears to be due to the increased incidence of bacteremia and endocarditis in already diseased persons rather than to an alteration in the character of the organism.[1] To appreciate the nature of the problem of staphylococcic bacteremia as an infection in older and often severely debilitated patients as well as in the young, it is necessary to consider the nature of both the organism and the patient. The purposes of this review are to re-examine the host-parasite relationship, to reconsider the important clinical aspects of bacteremia with and without endocarditis, and finally to discuss the methods of treatment that have met with greatest success.

STAPHYLOCOCCAL BACTEREMIA

The Organism

Staphylococcus aureus is responsible for more cases of endocarditis and bacteremia than any other organism save alpha and nonhemolytic streptococci.[2] While all staphylococci may cause serious infections, some are more virulent than others. The distinguishing features of these pathogenic strains were once considered to be the appearance of a ring of hemolysis around colonies growing on blood agar, and the production of a golden pigment. These are helpful but not entirely dependable criteria. The ability of the staphylococcus to produce coagulase is now regarded as the single most important indication of pathogenicity. It is demonstrated by the development of a coagulum in fresh human plasma after several hours' incubation with organisms from a 24-hour culture. The precise relation of coagulase to pathogenicity or virulence is undefined. Rammelkamp and Lebovitz[3] recently proposed that coagulase was of importance in modifying the host response to staphylococcal invasion. They suggested that coagulase, in action with reacting factor, was responsible for localizing infection and observed that infants, normally deficient in reacting factor, were not so capable of discrete abscess formation as adults. It is more generally believed that coagulase enhances the virulence of staphylococci by protecting them against the action of normal serum bacteriocidins and against phagocytosis.[4] Staphylococci that would not survive after entrance into the blood stream without coagulase can proliferate in its presence.

All pathogenic strains elaborate one or more of the many staphylococcal toxins or enzymes. In addition to hemolysins of 4 antigenically distinct types, staphylokinase, dermonecrotic toxin, enterotoxin, erythrogenic toxin, hyaluronidase, fibrinolysin, and a leukocidin are produced. The roles of enterotoxin, erythrogenic toxin, and the dermonecrotic or lethal toxin in clinical infection are self evident.

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This is not so true of the others. Their in vitro behavior is measurable but their actual mechanism of action in clinical infection is not clear. Staphylococci obtained from enclosed abscesses produce both staphylokinase and hemolysins in uniformly high titer. Coagulase-positive strains from healthy carriers in the hospital vary in toxin production but are nevertheless more toxigenic than those obtained from people outside the hospital area.[5]

The more highly toxigenic strains are apparently better able to establish themselves in normal tissues than others. While coagulase productivity is a way by which pathogenic strains in general can be separated from saprophytic ones, further gradations of potential virulence can be determined by the number and amount of the specific toxins they elaborate.

Although the various toxins are antigenic, their antibodies have at best a limited protective capacity. The course of acute infection in experimental animals was altered by the administration of anticoagulase antibody but the eventual fatal outcome was only delayed. Horse serum containing antibodies against the hemolysins, the lethal toxin, and possibly others, has been used in the past to treat infection in man, with occasional cures of cases of meningitis, pneumonia, and osteomyelitis.[6] There were, for example, 6 cases of meningitis with 4 recoveries. However, less favorable results have been observed by others, suggesting that antitoxins are of uncertain value in treatment of infections. Antibody formation does not occur in localized staphylococcal infections such as furunculosis in human beings, even when repeatedly due to the same strain. This has been attributed to the limited permeability of the abscess wall, which prevents the release of whole antigens into the circulation.[1] Penicillinase (perhaps a natural endowment of the organism from prehistoric times), is produced by some coagulase-positive staphylococci. As a specific penicillin-splitting enzyme, it does not account for resistance to other antibiotics; strains producing it, however, are more readily capable of acquiring resistance to other drugs.

The Epidemiology of Staphylococcal Infections

Specific identification of staphylococcal strains is essential to the determination of their distribution and for tracing the source of epidemic disease. Serologic differences among pathogenic strains led to the establishment of 9 subgroups in 1940. However, a more satisfactory technic now widely employed is typing with bacteriophage.[7, 8] Four broad subdivisions of coagulase-positive staphylococci have been established based on reactions with 19 distinct bacteriophages. Within each of these "phage-types" are strains which are lysed by one or more specific phages. Staphylococci are identified by the specific phages that exert this effect upon them; e.g., strain 42B is lysed only by phage 42B, while 6/47 is lysed by both 6 and 47. No correlation has been established between strain types and specific diseases with 2 exceptions: staphylococcal pneumonia complicating influenza was found to be primarily of phage type I while food poisoning was most frequently due to type III.[9]

The nose and throat of about 65 per cent of the normal population contain staphylococci of varying pathogenicity. The majority of these strains are penicillin-sensitive. The skin harbors these organisms in 20 to 30 per cent of people. Inside the hospital, however, the carrier rate in nose and throat as well as on the skin is increased by nearly 90 per cent. This is true of such hospital workers as nurses, orderlies, members of the house staff, and patients. The nares of newborn infants in hospital nurseries have been shown, in 90 per cent of cases studied, to harbor staphylococci that by phage typing were identical with the strain predominant in the hospital.[10] It has also been shown that they carry these strains for as long as a year after discharge.[11] The reservoir from which staphylococcal infections may be drawn is a large one, and the greatest concentration of organisms is in those areas where the most vulnerable people are to be found.

Despite antibiotic prophylaxis and treatment an increase in the number of postopera-

tive wound infections has been observed in many surgical wards. It was found that simple although rigidly enforced antiseptic technics in dressing wounds was followed by a significant reduction in the number of these infections.[12, 13] There was also a decrease in the number of staphylococcal carriers among the attending hospital personnel, and when the antibiotic prophylaxis of clean surgery was discontinued, it was found that fewer of these staphylococci were penicillin-resistant.

Whether one is within the hospital or outside it, infection does not develop simply because the organism is present. The organism must first be introduced into healthy tissues and overcome the normal physical barriers and humoral mechanisms that oppose bacterial proliferation. The first obvious barrier against infection is the intact skin and subcutaneous tissues. If staphylococci penetrate these defenses and enter the lymphatics or blood stream, phagocytes engulf them as do the fixed reticuloendothelial cells. A variety of naturally occurring substances in human serum exert a bacteriostatic or bacteriocidal effect. The importance of phagocytic activity was illustrated by Rogers,[14] who showed that the number of coagulase-positive staphylococci injected into the carotid artery of a rabbit was reduced 1000-fold within 20 minutes by trapping of bacteria within circulating phagocytes. Low grade bacteremia persisted despite this early phagocytosis because many of the organisms were not killed and were soon released. Obviously, the larger the number of organisms injected, the greater is the likelihood of continuing bacteremia. If only a small number of organisms enters the circulation, there is no particular danger to the normal person, but serious disease in the host or persistence of staphylococci at the point of entry may make even a small number dangerous.

Pathogenesis of Staphylococcemia

Staphylococci in a traumatized area of skin or within a localized infection of any tissue normally fail to enter the blood stream because of the activity of phagocytes or the presence of physical barriers. It has been shown that when they do so it is often by direct entrance into lymphatics.[15] No bacteremia occurs even when organisms are introduced in large amounts into a freshly opened wound in an experimental animal's extremity if the lymphatic drainage has been obstructed. There is evidence that in the presence of inflammation lymphatic channels remain patent or are actually widened. Thrombosis of small venous radicles has long been accepted as a tissue response to staphylococcal infection. Septic thrombophlebitis of these vessels has been shown to provide a source for the bacteremia that may complicate minor infections.[16] This intravascular focus for dissemination is an important mechanism by which emboli of organisms alone or of infected thrombin fragments enter the circulation in quantities too large to be controlled by phagocytosis or serum bacteriocidins. Denuding dermatoses provide a large surface area for contamination, while sutures that hold the edges of a wound together provide a small though unclosable portal of entry for bacteria. In addition to these, vesicular or pustular skin lesions, and the eczematoid rashes frequently evoked in children by contact with such irritants as kerosene and turpentine are also apt to be complicated by bacteremia. Ischemic ulcers in adults, particularly on the extremities of diabetic subjects, are often contaminated and may support the growth of numerous bacteria. If diabetes is poorly controlled, minor skin infections may become a serious threat to health, since even mild degrees of ketonemia interfere with the metabolic processes of granulocytes responsible for killing engulfed organisms. (The lactic acid production of neutrophilic cells has been shown to decline in the presence of ketone bodies.[17]) Once disorders of the skin were the most common of the predisposing diseases complicated by bacteremia, and their incidence was 30 to 50 per cent in most series. Whereas they are still a common cause when furuncles, carbuncles, burns, and abrasions are added to the lesions already listed, the frequency with which skin lesions are now com

plicated by endocarditis or bacteremia is decreasing, since blood-stream invasion can usually be prevented by appropriate therapy (table 1).

Intravascular infection developing within abscesses or more diffuse parenchymal inflammatory processes has been cited as a source for bacteremia of major importance. Osteomyelitis, pneumonia, and other infections are often followed by staphylococcemia on this basis. Recently more attention has been focused on the possibility of this complication developing from the thrombi that form about the end of metal cannulas or plastic tubing introduced in veins through incisions for purposes of administering fluids, antibiotics, or pressor substances.[18] Endocarditis, usually of the right heart, is a complication of the thrombophlebitis and superficial skin abscesses that develop on the arms and legs of narcotic addicts using contaminated needles and solutions for intravenous injections.[19] In contrast to the falling incidence of bacteremia due to skin infections, the number of cases following such intravascular infections is increasing, particularly among elderly or debilitated hospitalized patients.

The underlying cause of staphylococcal bacteremia in 15 to 20 per cent of cases prior to 1940 was osteomyelitis. It is currently responsible in only 2.4 per cent (table 1). Originating from trauma, skin infection, or even from bacteremia, osteomyelitis has always been difficult to treat even when recognized early in its course. While antibiotic treatment has reduced the incidence of complicating bacteremia, cases are still observed, especially in infants and in elderly patients. The diagnosis may easily be overlooked, since painful cellulitis of the underlying skin and subcutaneous tissues often masks its symptoms. In infants, who localize staphylococcal infections poorly, widespread osteitis complicating adenitis or cellulitis may develop rapidly and lead to deformity or to death.

Pneumonia is an important cause of staphylococcal bacteremia. Its incidence is unchanging yet the death rate is climbing. The redistribution of the disease from young and fairly healthy persons to aged, debilitated, and often terminally ill patients in the hospital accounts for the currently poor results of treatment.

Ineffective as antibiotic therapy of pneumonia may be, there has been a reduction in the incidence of complicating bacteremia. Of 238 cases of bacteremia compiled before 1942, 10.5 per cent followed staphylococcal pneumonia, while of 258 cases of bacteremia collected between 1952 and 1957, 6.6 per cent followed this infection (table 1). Staphylococcal pneumonia, which often complicates such common viral infections as measles, influenza, and poliomyelitis, may be followed

TABLE 1.—*Origins of Staphylococcal Bacteremia*

Years	1936-1942 (References 22, 29, 40)		1952-1957 (References 2, 18, 21, 31, 33, 41, 42)	
Number of cases	238		258	
Predisposing factors	No.	%	No.	%
1. Infection				
Skin	91	38.2	37	14.3
Respiratory tract	25	10.5	17	6.6
Mastoid	3	1.3	3	1.2
Bone	40	16.8	6	2.4
Urinary tract	15	6.3	13	5.0
Genital tract	7	2.9	17	6.6
Bowel	1	0.4	6	2.4
Teeth	3	1.2	8	3.2
Lymph node	1	0.4	1	0.4
Joints	1	0.4	1	0.4
Veins				
Cannula	1	0.4	3	1.2
Drug addiction			2	0.8
Septic phlebitis			2	0.8
2. Postoperative complications				
Surface wound infection	15	6.3	7	2.8
Respiratory tract			5	2.0
Genito-urinary tract			7	2.8
Prostate			31	12.0
Bone	4	1.6	6	2.4
Central nervous system			1	0.4
3. Undetermined	31	13.0	36	14.0
4. Undetermined but associated with other disease			47	18.2

by bacteremia in up to 50 per cent of cases. In the hospital serious staphylococcal pneumonia terminating in death from bacteremia often represents a superinfection in patients given antibiotic prophylaxis for such noninfectious processes as heart failure.[20]

Schirger and his co-workers[21] among others, have re-emphasized the hazard of bacteremia as a complication in the postoperative period, especially in the first few days. Thrombophlebitis, a contaminated suture, the leakage of bacteria-laden material onto exposed tissues, or the introduction of large numbers of organisms directly into the blood stream consequent to manipulation of infected tissues may lead to persisting bacteremia. In 1937 Skinner and Keefer[22] noted that bacteremia often followed incision and drainage of abscesses of the skin. This is no longer so true. At present bacteremia follows prostatic surgery more often than any other operation. In Schirger's group of 44 patients who developed staphylococcal bacteremia postoperatively 27 had had transurethral resection of the prostate. The degree of contamination of this organ, the trauma exerted in removing it, and the susceptibility of its venous plexus to thrombophlebitis are all contributing factors.

Clinical Manifestations of Staphylococcal Bacteremia

Patients with staphylococcal bacteremia can be grouped in 5 categories on the basis of their major symptoms: (1) symptoms due to the primary infection, (2) symptoms due entirely to bacteremia, (3) symptoms due to the metastatic suppurative lesions, (4) symptoms due to a combination of the three, and finally (5) those in which all symptoms are masked by a co-existing disease or suppressed by therapy administered in treatment. The manifestations of the infections range in degree from mild to fulminant.

1. Symptoms Predominantly of Primary Infection. Patients with staphylococcal pneumonia, meningitis, osteomyelitis, or other severe though localized processes normally have, in addition to the specific symptoms of these infections, high fever, leukocytosis, and rapidly developing anemia. They are often prostrate. Bacteremia is a common complication of each of these infections and may develop silently. The temperature often rises, the pulse rate becomes more rapid, and the patient may seem more gravely ill, but there is no more than an intensification of existing signs and symptoms.

If no treatment is given, or if it is inadequate, metastatic suppuration occurs or death follows a rapidly mounting fever and falling blood pressure. Given early enough, antibiotics can prevent bacteremia as a complication, or they can reduce the incidence of sepsis secondary to it (table 2). However, during the period before either of these occurs the presence of bacteremia may go undetected unless blood cultures have been obtained. Since this early phase of blood-stream invasion may last for days before specific signs of it are detectable clinically, recognition of its likelihood during any severe though localized infection is essential for its effective treatment.

While patients of any age may develop these serious staphylococcal infections of the lungs, meninges, or bone, it is usually in the very young or very old that the time interval between the development of this complication and death is shortest, and delay in the institution of specific therapy is most often disastrous.

2. Symptoms due Primarily to Bacteremia. The majority of patients with staphylococcemia probably belong in this category. Often, the source is a minor infection or an injury with only local discomfort. The entrance of micrococci into the circulation in these cases is usually accompanied by dramatic physical changes. The course of bacteremia may be subacute, acute, or fulminating. A small number of patients in all age groups (although most are derived from the extremes of youth and age) have an explosive illness, beginning and ending in the space of only a few days. The onset may be signaled by an abrupt chill with temperatures rapidly rising to 104 degrees and higher; diffuse muscular pains often follow. Soon, sometimes in hours, the pa-

tient is prostrate, exhibiting changes in the sensorium ranging from confusion or somnolence to coma. Infants occasionally exhibit a peculiar pallor associated with rapid respirations and tachycardia. Adults, on the other hand, display either no visible color change or show marked facial suffusion. The blood pressure is at first maintained but soon falls, rarely to be revived. Terminally, purpuric lesions may appear on the skin and are found in some cases to be associated with hemorrhage in the adrenal parenchyma. Widespread lesions may be demonstrated at postmortem study in such cases, but the course of the disease is so swift that they are rarely manifested openly.

The majority of patients, though severely ill, are not so rapidly devastated. As in the preceding group the onset of bacteremia is sudden, with fever and chills or chilly sensations predominating at first. Soon afterwards, the patient feels sick and often has moderate to marked pain in the larger joints without swelling or local tenderness. There are often diffuse muscular aching pains, persistent headache, sweatiness, and loss of appetite or actual nausea and vomiting. But for the fever, there are no physical changes other than those associated with the underlying infection. Fever in this group, while characteristically high, may vary from sustained high temperatures to a swinging "septic" pattern and uncommonly is observed to be intermittent. In a number of patients symptoms may persist without change for a week and occasionally longer before other evidence of bacteremia develops.

A small group of patients have only mild symptoms and signs produced by the intermittent release of small numbers of staphylococci into the circulation. Low-grade fever with a normal diurnal curve is observed in association with milder variants of the symptoms presented above; anorexia, insomnia, and slight general discomfort without localization are also common. Symptoms of this type have been known to persist for as long as 4 or 5 months before a diagnosis could be established, even without antibiotic suppression.

TABLE 2.—*Metastatic Lesions in Endocarditis or Bacteremia*

Year of report	1926	1939	1955	1957
Number of patients	24	35	38	109
Bacteremia only		+		+
Bacteremia and endocarditis	+		+	
	Number of lesions			
Location and type of lesion				
Central nervous system	20*	7*		
Meningitis			7	2
Cerebral infaret			1	
Cerebral hemorrhage			1	
Epidural abscesses				2
Focal abscesses				20
Kidney		25*		
Pyelitis and pyelonephritis			3	
Glomerulonephritis	8		4	
Renal abscess			1	
Blood vessels				
Adrenal hemorrhages			1	
Arterial thrombosis			1	
Mycotic aneurysm			3	
Local thrombosis			1	
Heart	19	4*		
Pericarditis	5		3	1
Myocardial abscesses	14		1	
Ventricular aneurysm			1	
Lungs	11*	24*		
Pneumonia	.		3	3
Pulmonary embolus			1	
Pulmonary infaret			3	
Lung abscess			2	
Bones and joints				
Arthritis	6	4		1
Osteomyelitis		1		
Subacromial bursitis		1		
Skin		10*		
Liver		2*		
Gastrointestinal		5*		

*Figures obtained from reports not specifying individual lesion observed.

Antibiotic therapy may actually convert an acute, though often undiagnosed bacteremic process into a slowly progressive, less symptomatic one of this type. When the presence of organisms in the blood stream accounts for all the symptoms the underlying infection is often relatively insignificant. Peripheral thrombophlebitis, furuncles, superficial wounds or suture infections, and pyoderma associated with an underlying dermatosis are common

examples of the primary focus. Similarly, bacteremia complicating surgery of the prostate or elsewhere is not likely to be masked by the symptoms due to disease in the traumatized area. The variability of the response to bacteremia is such that unless the diagnosis is considered when the only major symptom is fever it will often be missed until late in its course. The presence of leukocytosis in association with fever suggests bacterial infection, but not its origin; migratory joint pains may suggest the diagnosis of arthritis. Low-grade fever may even be dismissed as unimportant if not accompanied by other evidence of disease. An example is the case of a woman who received x-irradiation for a pelvic malignancy and developed an eczematoid skin eruption over the lower abdomen. Daily fever to 100.2 degrees occurred a week later, and, in association with anorexia, represented the only symptom of a low-grade bacteremia. The diagnosis was verified by 3 successive blood cultures obtained for evaluation of her "obscure fever." Treatment with antibiotics chosen on the basis of the organism's sensitivity resulted in a prompt decline of temperature to normal levels, sterile blood cultures, and a return of her appetite.

3. Symptoms due to Metastatic Lesions. Septic emboli that lodge in the vessels of the heart, the lungs, the central nervous system, and other organs can produce dramatic symptoms that may be the first noticeable evidence of bacteremia.

Pulmonary Symptoms. Many patients with endocarditis involving the tricuspid or pulmonic valves as well as those with bacteremia and no endocarditis have symptoms of dyspnea, chest pain, tachypnea, or hemoptysis as a first major indication of infection.[23]

Although fever had been present for a day, sudden spiking of fever with chills and severe dyspnea were the first alarming signs that occurred in an 18-year-old girl with facial cellulitis complicating a small pimple. Her chest was clear to physical examination, but an x-ray showed many small, fluffy, nodular infiltrates throughout both lung fields. Although the staphylococcus in her blood stream was sensitive to the antibiotics employed, she succumbed to this infection, which had started under the mantle of oral tetracycline therapy given for the cellulitis. Abscesses were present in the myocardium, the liver and the spleen, but the lungs were the site of the most extensive changes. Non-fatal pulmonary infarcts with recurring episodes of fever, cough, and occasional hemoptysis may be the only early symptoms of staphylococcemia.

Two types of pulmonary lesions are observed. One as in the cited case history, is composed of numerous miliary abscesses producing widespread changes easily visible on chest x-rays as softly outlined, rounded infiltrations. Associated with these focal parenchymal abscesses is the generalized inflammatory reaction that accounts for the degree of dyspnea. Purulent bronchitis and pulmonary edema are frequently found at autopsy. The other important type of lesion is pulmonary thrombophlebitis. Suddenly developing chest pain, cough, and occasionally hemoptysis may follow the lodging of emboli, but it is seldom that such manifestations are the dominant initial symptoms of bacteremia without endocarditis. In the presence of endocarditis, large emboli may occur and not infrequently produce major pulmonary infarction.

Central Nervous System Symptoms. Weakness associated first with fever and later with unresponsiveness were the principal manifestations in an elderly man with mild diabetes and a few furuncles.[24] Blood cultures yielded *Staphylococcus aureus.* It was shown at autopsy several days later that he had succumbed to "brain purpura" characterized by extravasated blood and necrosis in pericapillary and perivenular areas (pericapillary encephalorrhagia). Many different neurologic syndromes arise as a result of cerebral vascular occlusion. Common among the first signs are sudden hemiplegias or cranial nerve palsies, personality changes, and psychotic behavior. Combined brain and cord disturbances may occur. A man with chronic lung disease developed headache, fever, and diplopia followed by weakness in both lower extremities that progressed upward to involve

he chest. The presence of a sensory level nd the weakness suggested a cervical epidural bscess. Myelography demonstrated an obtructive lesion at the level of the second cerical vertebra. Decompressive laminectomy as carried out with immediate though transent relief of symptoms. The spinal fluid, hich had been xanthochromic, became purulnt within hours when the obstruction was elieved allowing communication of intraranial with lumbar intrathecal cerebrospinal uid reservoirs. He was found to have had subdural abscess that had produced, by extnsion of inflammatory edema, compression f the cervical cord. The signs of the verified staphylococcal bacteremia were entirely masked by the central nervous system disorder. Specific, intensive antibiotic therapy in this case was of no avail.

The importance of considering the possibility of bacteremia in cases of obscure febrile central nervous system disorders can for this reason scarcely be overstated. Diagnoses of "encephalitis," or "aseptic meningitis," or even of "subarachnoid hemorrhage," particularly in the young, should be regarded with suspicion and cultures of the blood obtained to ensure that bacteremia be not overlooked.

Symptoms Related to the Cardiovascular System. Endocarditis, with its pathogenesis and clinical manifestations, will be discussed separately below. The symptoms of cardiac involvement may dominate the bacteremic syndrome in many cases. Discrete abscesses of the myocardium and interstitial myocarditis may occur without endocardial localization but do not necessarily produce functional aberrations. Although the commonest and most important signs produced by these lesions are those associated with heart failure, whether these are due more to intrinsic cardiac damage than to concomitant fever, tachypnea, and pneumonia is difficult to assess.

Pericarditis often mimics pneumonia. Fever, cough, and dyspnea are coupled with moist rales and a friction rub. Enlargement of the area or cardiac dullness, alteration in the configuration of the heart shadow on x-ray, and electrocardiographic abnormalities all help in the diagnosis. In some, an urticarial rash, hepato-splenomegaly, and dyspnea are the presenting symptoms.[25] Signs of constriction or tamponade may appear if the effusion develops rapidly, even when the total amount of fluid is small. Pericardial fluid may be sterile or purulent. While generally regarded as a serious complication, it is of interest that recovery from purulent pericarditis with tamponade has been known to follow treatment consisting only of transfusion, pericardial aspiration, and small doses of a soluble sulfonamide. Pericarditis of nontuberculous origin is most commonly produced by staphylococci,[25] and while it more commonly follows pneumonia than bacteremia, it is still an important complication of the latter.

Mesenteric thrombosis, popliteal aneurysm, and axillary thrombosis are examples of the peripheral vascular complications of staphylococcal bacteremia.

4. Symptoms from a Composite of Initial Lesion, the Bacteremia and the Metastatic Suppuration. Patients in this category have usually had for a short time a localized infection without constitutional signs and develop suddenly major symptoms of fever and chills coincidentally with the appearance of a varying number of embolic manifestations. Often the first or primary infection is regarded as unimportant, as in the case of a pimple or small furuncle. Occasionally the local symptoms obscure the nature of the initial process as when pain is the only sign of a deeply situated suppurative process. An example of this is the case of a 40-year-old woman with hip pain for a week who developed within 48 hours fever, chest pain, headache, and a vesicular skin eruption. The disease, from which she recovered, consisted of a suppurative arthritis, meningitis, pulmonary infarction, and embolic lesions of the skin.

Another example is a boy who injured his neck while wrestling. In the next week, he developed spiking fevers, delirium, diarrhea, headache, and a swelling near the site of injury. At the time of admission to the hospital he had a swollen, red, and tender left ankle. There was a lymphocytic pleocytosis

TABLE 3.—*Constitutional Response to Bacteremia*

Year of report	1957 (21)		1957 (33)		1952 (2)		1942 (22)	
Number of patients	109		55		25		122	
Bacteremia only	+						+	
Bacteremia and endocarditis			+		+			
	No.	%	No.	%	No.	%	No.	%
Fever	103	94	37*	67	25		122	
Septic								82
Intermittent								14
Low grade								4
Chills or chilliness	44	40			11	44	30	
Arthralgia	14	13			2	7		
Nausea and vomiting	41	38			9	36		
Change in sensorium	42	39						
Hypotension	4	4	5	9				
Leukocytosis†	65	60						
Anemia‡	51	47						
Diarrhea					2	7		
Sweating	13	12						
Leukopenia	6	6						
Hypothermia			1	2				

*Over 102 F.

†Over 10,000/mm.^{3}

‡Under 12 Gm. if men or under 11 Gm. if women.

of the spinal fluid, a peripheral leukocytosis and a systolic murmur without evidence of cardiomegaly. Blood cultures yielded *Staphylococcus aureus*. He was placed on antibiotic therapy and the mass in his neck, which became fluctuant, was drained. He recovered, but before treatment was concluded it was demonstrated that he had cervical osteomyelitis (presumably a complication of the abscess), suppurative arthritis of the left ankle, and a nonsuppurative parameningitis, but no evidence of endocarditis. The time interval separating the development of each of these metastatic lesions was so short that each contributed to the general constitutional reaction.

5. Presence of Bacteremia Masked by Therapy Directed at an Underlying Disease. Attention has been drawn to the peculiar danger in patients treated with adrenal steroids that have denuding skin diseases such as exfoliative dermatitis.[1] Already deprived of the important skin barrier against the entrance of surface staphylococci, their jeopardy is increased by steroid treatment, which both impairs local tissue defenses and suppresses the constitutional response that heralds invasion of the blood stream. The administration of tetracyclines prophylactically in these cases has been shown to enhance rather than to reduce the likelihood of staphylococcal infections by eradicating other organisms and increasing the number of staphylococci.

Steroid therapy of leukemia, chronic obstructive emphysema, nephrosis, rheumatoid arthritis, and allergic disorders increases the danger of bacterial infection, although the peculiar vulnerability to staphylococcal invasion seen in those with skin disease is not present. Because of the nature of the underlying disease, however, the prognosis is far worse should infection develop. In leukemia, for example, even so benign an infection as pharyngitis may be complicated by bacteremia.

Incidence of Specific Signs and Symptoms of Staphylococcal Bacteremia

It is of interest to review the incidence with which the various signs of the disease are encountered based on many reports from the years before and including the antibiotic epoch (table 3).

Metastatic Infections Associated with Staphylococcal Bacteremia

The outcome of persisting staphylococcal bacteremia in untreated cases is almost always death. In some there may not be time fo

the development of metastatic lesions; in others bacteremia may actually clear after metastatic suppuration is established and, rarely, both bacteremia and distant infections are cleared and there is recovery. If survival is long enough, metastatic infection is almost inevitable: of 122 cases assembled before 1942 (22), 100 developed suppurative lesions in parts remote from the point of origin of the bacteremia. The incidence of metastatic sepsis has been reduced since that time, presumably by antibiotic treatment (table 2). It can be seen that once one metastasis has been produced, others are far more likely to occur. The primary sites of infection from which most metastatic lesions are derived are the heart valves, bone, and the lungs.

Central Nervous System Involvement

The localization of organisms in the brain, the cord, or in their investing membranes is a serious complication. Mycotic aneurysms occur less often than in streptococcus viridans infections,[26] but focal miliary abscesses are quite common. The ability of staphylococci to invade normal tissues, to proliferate in them and to produce destructive lesions without the necessity of platelet and fibrin plugs to protect them against phagocytic action probably accounts for the many suppurative infarcts.

In brief, 4 specific alterations arise when staphylococci enter the cerebral circulation:[27] simple vascular occlusion from masses of platelets, fibrin, and organisms; vascular occlusion due to focal intimal infiltration; pericapillary and perivenular hemorrhage ("brain purpura"); and localized or diffuse suppuration in the form of miliary abscesses along the course of the blood vessels or as a subdural empyema or meningitis.

The over-all incidence of lesions within the brain and its investments in cases of bacteremia was 20 per cent prior to antibiotic therapy and 3.6 per cent thereafter. In cases of endocarditis the incidence as reported by Thayer[28] in 1926 in a series of 24 cases was 8 per cent. Not all of these lesions were symptomatic, many being small localized abscesses discovered at necropsy. Only 2, (8 per cent) had meningitis. After antibiotic therapy became available, there were more survivors of endocarditis and among them it is impossible to estimate the true incidence of clinically inapparent abscesses. The reported over-all incidence of central nervous system involvement is 24 per cent (table 2).

Respiratory Tract Involvement

The lungs are at once the site of primary staphylococcal infection, a repository for organisms spread by the blood stream, and a source for the dissemination of emboli to other tissues. The frequency of pulmonary embolizations large enough to produce symptoms or radiologic signs is far less than the actual incidence of lesions demonstrable at autopsy.

The commonest event is pulmonary embolism with the development of abscesses ranging upward from microscopic size. Infarction of significantly large segments of lung is less often observed. Before antibiotic therapy, the incidence of demonstrable changes of all types in the lung was nearly the same in cases of bacteremia with endocarditis as in those without endocarditis.[28, 29] There were only 3 cases among 109 antibiotic-treated patients with bacteremia.[21]

Involvement of the Kidney

Renal lesions are commonly associated with bacteremia, and the presence of gross or microscopic hematuria is regarded as a valuable laboratory aid to its diagnosis. Focal embolic glomerulonephritis produced either by the presence of small but obstructive emboli, or by an intrinsic fibrinoid reaction of renal vessels is not a complication observed during the course of endocarditis due to staphylococci; it is common, on the other hand, in endocarditis due to pneumococci, gonococci, and to hemolytic streptococci. In his description of glomerular lesions associated with endocarditis, Bell[30] pointed out that it was uncommon to find focal embolic lesions before 6 weeks had elapsed. Staphylococcic valvulitis usually terminated fatally before this.

Involvement of the Heart

Cardiac involvement complicating bacteremia is a serious complication primarily be-

TABLE 4.—*Incidence of Pre-Existing Heart Disease in Cases of Staphylococcal Endocarditis*

Author	No. of patients	With previous heart disease	No previous heart disease known
Wilson et al.[33]	35	29	6
Fisher et al.[31]	38	21	17
Dowling et al.[2]	77	32	45
Total	150	82	68
Per cent	100	55.3	44.7

cause of an increased frequency of metastatic suppurative lesions and only secondarily because of the injury to that organ or its valves.

In addition to endocarditis, suppurative inflammatory changes occur in the pericardium and in the myocardium (both as interstitial myocarditis and focal abscesses). It is likely that the myocardial changes are in some cases responsible for congestive failure or pulmonary edema, particularly when associated with pneumonia. Acutely developing ventricular aneurysm is another complication.[31] In some instances the clinical evidence of cardiac metastasis is limited to electrocardiographic alterations termed by some[29] "toxic myocarditis." The actual incidence of myocarditis of this type is uncertain because of the failure to obtain electrocardiograms routinely in all cases of bacteremia.

Pericarditis was not observed by Mendell[29] in his series of 35 patients with untreated bacteremia, but was demonstrated in 5 out of 24 cases of endocarditis reported in 1926. A single case of pericarditis was observed out of 109 treated cases of bacteremia[21] while there were 3 cases out of 38 treated cases of endocarditis.[31]

Involvement of the Bones and Joints

Transient though often severe joint pains have been mentioned as one of the manifestations of acute bacteremia. When sequestration of staphylococci within the articular spaces or the marrow cavity of long bones occurs, destruction of cartilage in the joint may lead to permanent deformity. X-ray evidence of localization may appear within 24 hours. Actual osteomyelitis is uncommon. However, in infants under the age of 1 year, osteitis characterized by periosteal proliferation, and absence of sequestration and involvement of more than one bone may develop rapidly and poses an important threat to the future development of the involved extremity.[32]

Involvement of the Skin

It is difficult to determine the incidence of petechiae, vesicles, and furuncles associated with bacteremia because they are not commonly mentioned in reports of series of cases. Of recent studies, the most detailed description of the skin lesions was provided by Wilson et al.[33] in a review of 55 cases of both bacteremia and of endocarditis. They noted a wide variety including scarlatiniform, urticarial, morbilliform, and purpuric rashes. Erythema multiform and nodose lesions were also encountered. More typical of staphylococcal bacteremia than these are subcutaneous and superficial abscesses. In some, these lesions resemble the rash of chickenpox, having a red base and a central vesicle filled with only a slightly cloudy fluid. They do not always contain organisms, and in healing may leave a shallow black eschar. These lesions are the result of capillary and venular thrombosis similar to that seen in the Schwartzman reaction.

The skin lesions do not as a rule confuse the diagnosis, although I have seen 2 cases of bacteremia in which the initial diagnoses were measles and chickenpox.

Involvement of the Blood Vessels, Liver, and Spleen

In addition to the embolic phenomena in various organs, the major vessels of the extremities as well as in the viscera may be involved. Peripheral gangrene of the nose has been described, as well as thrombosis of the axillary artery and mycotic aneurysms of the popliteal artery. There were 5 significant vascular lesions in a group of 38 cases of endocarditis.[31]

Metastatic sepsis or emboli are not limited in their distribution to the organs already mentioned. Focal abscesses or zones of necrosis have regularly been observed in the liver, and mesenteric thrombosis and splenic infarcts may occur. Perisplenitis may produce

TABLE 5.—*Localization of Endocarditis in 173 Cases*

Author	Congenital defect	Mitral	Aortic	Mitral aortic	Tricuspid	Pulmonary	Tricuspid pulmonic	Tricuspid pulmonic aortic	Other valve combination	Total
Dowling[2]	3	41	16	16	17	2	0	1	4	100
Fisher[31]	6	13	5	5	5	0	3	1	0	38
Wilson[33]	3	14	7	10	1	0	0	0	0	35
Total	12	68	28	31	23	2	3	2	4	173
Per cent	6.9	39.3	16.2	17.9	13.3	1.2	1.7	1.2	2.3	100

a friction rub and pain in the left upper quadrant of the abdomen.

The involvement of the liver is usually inapparent and detectable only at necropsy. Although jaundice is occasionally an early manifestation of bacteremia as a result of massive hemolysis, I have seen it develop during the second week of treatment for bacteremia associated with chemical evidence of parenchymal damage indicated by elevated alkaline phosphatase, cephalin flocculation, and thymol turbidity.

STAPHYLOCOCCAL ENDOCARDITIS

"Acute infective" or "ulcerative endocarditis," usually the result of staphylococcal valvulitis, connotes a rapidly progressing destructive lesion on the heart valve with acute onset of fever and even prostration, and an early fatal outcome.[34] Occasionally staphylococcal infections of the endocardial surfaces may be quite slow in their evolution and produce few symptoms other than occasional fever for periods of months. The acute disease may be converted by suppressive antibiotic therapy into a subacute process.

Two features of staphylococcus endocarditis are of particular importance, i.e., the propensity of the organism to invade normal heart valves, and the frequency with which only the right side and particularly the tricuspid valve is involved. While antibiotics are responsible for reducing the incidence of pneumococcal or gonococcal endocarditis, both of which may involve undamaged valvular surfaces, they have not so affected the incidence of staphylococcal infection.

Pathogenesis of Endocarditis

Bacteremia from any site may lead to endocarditis. Bacteremia need not be prolonged as in prostatic surgery complicated by endocarditis, nor need it be massive; pharyngitis may be complicated by bacteremia and endocarditis, particularly if there are underlying valvular deformities.

In the presence of focal deformities of the heart valves, septa, or immediate outflow tract, there may be abnormal turbulence and associated endocardial fibrosis which enhance the likelihood of bacterial sequestration.[35] This may effectively reduce the length and intensity of exposure necessary to produce endocarditis.

Over half the reported cases of staphylococcal endocarditis occurred on previously damaged valves (table 4). The type of deformity varies somewhat with the age of the patient; thus congenital lesions are far more likely to be present in younger patients, while as age increases the incidence of rheumatic heart disease, arteriosclerosis, and syphilitic aortitis becomes greater. The mean age of patients with underlying congenital heart disease was 20 years, and for patients with rheumatic heart disease, 44 years.[30, 33] In a series of 173 cases of all ages the incidence of congenital lesions was 6.9 per cent.

Table 5 shows the frequency with which each valve was involved. Rightsided endocarditis among narcotic addicts rose sharply after 1940,[19] especially among users of heroin who often used it mixed with other contaminated materials.

Clinical Manifestations of Endocarditis

Over 30 years ago Thayer[28] called endocarditis a "mere incident in the course of a generalized septicopyemia." He was not belittling the importance of the valvular lesion, but considering its relative importance as a cause of death. Of the 26 patients he studied,

TABLE 6.—*Embolic Complications Associated with Staphylococcic Endocarditis (from Thayer)*

Lesion	Incidence	
	Number	Per cent
Myocarditis	14 (of 20)	70
Myocardial abscess	11 (of 20)	55
Pericarditis	5	19.2
Pneumonia	11	48.2
Nephritis	8	30.7
Arthritis	6	24.0
Petechiae	4	16.0
Cerebral emboli	2	7.6
Meningitis	2	7.6
Total no. of patients	21	80.7

17 died of overwhelming infection, while only 1 died as a specific result of endocardial involvement. The remainder succumbed either to emboli to the brain or lungs or to other severe underlying diseases. The importance of Thayer's description is in its emphasis that the majority of the signs and symptoms of endocarditis are those associated with bacteremia and it is often not until late in the course of the infection that the specific valvular lesions produce recognizable abnormalities. One result of antibiotic therapy, even when unsuccessful in salvaging life, has been to prolong the course of the disease long enough for these abnormalities to develop.

While the major clinical features of endocarditis are similar to those already cited for bacteremia, certain of them suggest the diagnosis of endocarditis. There are also important differences between this type of endocarditis and that produced by such less invasive organisms as *Streptococcus viridans.*

The onset of symptoms of infection may antedate changes due to valvular involvement for as short a period as a day or for as long as several weeks or even months. Important manifestations, however, may appear quite rapidly. Suddenly appearing fever followed quickly by heart failure and the development of an aortic diastolic murmur is not infrequent in endocarditis. Earlier writers have stressed the importance of a pericardial friction rub and embolic phenomena in the skin, joints, or lungs as important evidence of endocarditis,[29, 34] but none of these complications depends on the presence of valvular infection for its production. As with any kind of endocarditis, the most important diagnostic criteria are the development of a murmur of any type (including the addition of new heart murmurs), embolic suppuration, and the demonstration of bacteremia. Anemia and splenomegaly are usually not present at first, but either may develop rapidly. Clubbing of the fingers does not occur.

It has been observed that a peculiar syndrome frequently suggests the diagnosis of endocarditis in infants.[36] It consists of pallor with tachypnea, intermittent cyanosis and fever without evidence of pulmonary disease or obstruction sufficient to account for these changes. Pallor alone, of course, has been observed in infants with staphylococcal pneumonia or other overwhelming infections.

Occasionally, specific metastatic complications of endocarditis help in making the diagnosis. Arterial obstructive lesions in such major vessels as the axillary or popliteal arteries, or in such smaller ones as the dorsalis pedis, indicate large emboli probably from the heart. Massive pulmonary infarcts or repeated small ones suggest, though less reliably, embolization from the right heart. Cockayne[37] described a woman who was perfectly well until chest pain and vomiting suddenly occurred and were followed within the next seven days by arterial emboli to a foot, one hand, and the nose. She died on the seventh day because of a pulmonary infarct, and had a large aortic vegetation. There was nothing in her history to suggest where the disease had actually started or even from what point bacteremia had developed. Another patient was a young woman sent to the hospital with signs suggesting a pericardial effusion who died very shortly thereafter with a massive pulmonary infarction and a vegetation on a congenitally unicuspid pulmonary valve.[38] Multiple embolic lesions also suggest endocarditis, even without an audible heart murmur.[39] Representative of the frequency of various embolic lesions is the incidence compiled in the study by Thayer[29] (table 6).

Whereas pulmonary emboli with sterile blood cultures have been considered a dominant feature of right-sided endocarditis, this was not true in the experience of Bain et al.[23] in a study of 21 autopsied cases. Pulmonary abscesses or infarctions were present in 80 per cent and a similar percentage had positive blood cultures during life. It is likely that the organisms found in the systemic circulation arose from the many small abscesses found within the lung substance. Bacteria but not embolic fragments may easily pass through the pulmonary circulation. It would appear, then, that there are 2 possible explanations for peripheral bacteremia in cases of tricuspid endocarditis. Bacteria may enter the circulation by passing through the lung filter, or if trapped there, may be disseminated from resultant focal pulmonary infection. The importance of an assiduous effort to isolate organisms from the blood stream in cases of suspected infection of the tricuspid or pulmonic valve is thus emphasized. The reward is the immeasurable advantage of identifying the causative organism and its sensitivity, and of establishing with greater certainty a diagnosis of endocarditis, which otherwise is easily missed because of the inconstancy of murmurs. The tricuspid valve is involved more often than the pulmonic valve in cases of staphylococcic endocarditis, and when murmurs are produced, they are frequently overlooked or regarded as the product of fever and tachycardia. Pulmonic murmurs are more accurately ascribable to the proper valve, and the proper diagnosis is more readily made.

According to Thayer,[29] subacute staphylococcal endocarditis was associated with albus strains only. Since 1926, however, infections of this type due to *Staphylococcus aureus* have been observed. The clinical course of the infection does not differ from that produced by *streptococcus viridans* or other organisms of poor invasive potentialities, but it may rapidly be converted into a fulminating one. In case reported by Geraci and Martin[39] the illness was protracted over a period of 4 months with low-grade fever and malaise as the major symptoms; then sudden spiking fevers with chills appeared, an aortic diastolic murmur was heard, and despite carefully planned therapy, death occurred from a cerebral embolus. The importance of the proper interpretation of staphylococci appearing in the blood cultures is here emphasized. "Saprophytic" strains in the blood stream of patients with a disease bearing any resemblance to endocarditis must be regarded seriously.

The Treatment of Staphylococcal Bacteremia and Endocarditis

Many new antibiotics have been marketed recently for therapy of staphylococcal infections and particularly for cases in which resistance to better known agents has been demonstrated. Too short a period of time has elapsed to assess either their value or their undesirable side reactions. Persistence of the high mortality rate in treated cases is in part due to the increasing number of patients in whom bacteremia represents a terminal complication of a severe underlying disorder and for whom the antibacterial activity of the drugs used is not enough to effect a cure. There are, nevertheless, many cases in which cure is possible because of new antistaphylococcal agents.

The factors that determine the plan of therapy are numerous, but the most important is that the drug or combination of drugs chosen be the one to which the organism is most likely to be sensitive. Of great importance too is the selection of agents least likely in themselves to be of danger to the patient if given for prolonged periods of time.

It is generally agreed that penicillin represents the most satisfactory antistaphylococcal agent when the organism is sensitive to it. Its current wide usage has reduced its value in hospital-acquired infections, since the majority of staphylococci in this area are no longer sensitive to clinically attainable concentrations. So high is its therapeutic index, however, that in many cases penicillin can be used even when, by some criteria, the organism is considered a resistant one. Thus the fact that greater than 10 units per ml. of penicillin may fail to suppress staphylococcal

growth on a blood agar plate does not mean that the agent cannot be used, since it is possible by giving large amounts to obtain blood levels in excess of 50 units per ml. Disk-sensitivity determinations employ concentrations no greater than 10 units of the drug and may be quite misleading, therefore, and it is often necessary to use the cumbersome but more accurate tube-dilution technic, which can define the precise amount of drug needed to exert bacteriocidal or bacteriostatic activity in vitro. Such information, however, is not as a rule available at the time treatment is begun, and the initial choice of drugs must often be made without recourse to sensitivity tests of any type.

Penicillin is the drug of first choice for management of infections developed outside the hospital in the absence of specific knowledge of the organism's sensitivity because 90 per cent of the strains thus acquired are susceptible. It should not be used in the treatment of hospital-acquired infections, however, unless it can be shown that the infecting strain is one of the susceptible 10 to 20 per cent among the hospital population of organisms. If penicillin is used, it must be given either intramuscularly or intravenously, and the aqueous crystalline benzyl salt either of sodium or potassium should be employed. It is important in choosing the penicillin preparation to remember that there is a gram of either potassium or sodium chloride in every 10 million units.

The dose of penicillin and the frequency with which it should be given depend on the age and size of the patient and the nature of the process. For a superficial skin infection with bacteremia and no endocarditis, 2 to 4 million units of an aqueous crystalline benzyl penicillin G daily are adequate. This can be given by intramuscular injection every 4 to 6 hours or it can be given by hypodermoclysis with aliquots of the daily dose diluted in saline being delivered at the appropriate time intervals. If the underlying infection is more deeply situated, larger doses of penicillin should be given to ensure adequate tissue levels at the site of localization. Depending on the severity of the infection as determined by the constitutional response and the extent of involvement, from 4 to 20 million units a day may be necessary. In overwhelming infections it is wise to use more than one drug. One important reason for this is to reduce the chance of encountering a strain resistant to the agent employed, and another is that the bacteriocidal activity of the drugs combined may be greater than that of either one alone regardless of the dose used. Streptomycin, uncommonly used in treating staphylococcal infections, is apt to be an exceedingly good agent in both respects. It is used in full therapeutic doses of 20 to 30 mg./Kg. every day.

If infection had developed in the hospital, it is not safe to assume that either of these 2 drugs will be effective, and others must be employed. Presently, the majority of hospital strains are sensitive to chloramphenicol and erythromycin. Of the 2, erythromycin is the better agent and the addition to it of other drugs does not enhance its bacteriostatic activity. However, staphylococci may exhibit increasing resistance to erythromycin when this agent is used by itself. Chloramphenicol suppresses the rate with which this occurs. The dose of the two is the same (50-75 mg. per Kg.). Both should be given parenterally to ensure adequate tissue concentrations. In the prostrate patient oral administration is often less satisfactory as judged by clinical observation.

When infection has developed during antibacterial therapy or prophylaxis, it must be assumed, in the absence of knowledge of its drug sensitivity, that none of the agents previously given the patient will be of value. Potent but often toxic agents such as bacitracin and neomycin can be used under these circumstances.

Among the more recently developed antibiotics that have good antistaphylococcal properties are novobiocin, vancomycin, kanamycin, and ristocetin. All are new enough in the treatment of stapylococcal infection that sensitivity to them can often be safely assumed. Overwhelming infections have been

ured under treatment with each of these drugs. The decision as to which of these agents should be employed is necessarily based on determination of in vitro sensitivity of the organisms. Not enough experience has yet been collected to determine which of these antibiotics is superior. Both vancomycin and kanomycin have theoretic advantages in that bacteriocidal activity has been demonstrated in each. Only extensive clinical trial will decide whether this is an important advantage or not.

Surgical drainage of enclosed abscesses is an extremely important part of therapy as indicated by the fact that before antibiotics the majority of survivors of severe staphylococcal infections were patients with enclosed lesions that could be drained.

Once the disease is controlled, the duration of the therapy is determined by the nature of the infection. If the initial lesion is a superficial one and bacteremia occurs without endocarditis only 2 to 3 weeks may be required. When bacteremia complicates a more deeply situated infection, treatment must be continued longer. If osteomyelitis, suppurative arthritis or endocarditis is present, 4 to 6 weeks or even more are usually necessary. The period of treatment is best dated from the time when clinical response is first observed rather than from the actual onset of therapy.

Summary and Conclusions

Staphylococcal bacteremia and its complication, endocarditis, are discussed from several viewpoints. A delineation of the factors that determine virulence of the organism and of those that determine host susceptibility is undertaken, and the manifestations of staphylococcemia as they are encountered in practice are classified with an analysis of the incidence of its signs and symptoms.

Staphylococcal bacteremia and endocarditis have been thrust into a position of prominence by the advent of successful therapy for other bacterial infections. A decline in their incidence among young people with localized staphylococcal infections has been balanced by an increase among elderly, debilitated, or very young patients within the hospital. Antibiotic therapy is responsible for the prevention of staphylococcemia in a significant number of cases on the outside, but for a variety of reasons it has not been so effective in the management of hospitalized patients. Staphylococcal infections contracted within the hospital are almost always caused by the organisms harbored there. These strains have survived exposure to many of the antibiotics used in the individual hospital. The majority of them are coagulase positive and elaborate one or more of the specific toxins and are, therefore, the ones most capable of producing serious infections. This infelicitous concentration of virulent microorganisms in areas where the most susceptible people are cared for accounts in part for the frequency of complicating staphylococcal infection.

What differences there are in the prognosis of hospital and home acquired infections are accounted for by the character of the organism in these 2 locations and by the type of patient, particularly with respect to age and the presence of other disease.

The protection of hospitalized patients by rigid antiseptic technic and early and intensive treatment of staphylococcal infections in all patients can do much to reduce their danger, but the solution to the problems of the continued high mortality rate depends at least as much on a better knowledge of the factors that determine virulence within the organism and susceptibility within the patient as it does on the development of new and potent antibiotics.

Acknowledgment

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Summario in Interlingua

Bacteremia staphylococcal e su complication, endocarditis, es discutite ab plure punctos de vista. Es interprendite un delineation del factores que determina le virulentia del organismo e del factores que determina le sus-

ceptibilitate del hospite. Le manifestationes de staphylococcemia, in tanto que illos es incontrate in le practica, es classificate como bas de un analyse del incidentia de su signos e symptomas.

Bacteremia staphylococcal e endocarditis occupa un position de prominentia depost le advento de efficace therapias pro altere formas de infection bacterial. Un reduction de lor incidentia in juvene patientes, qui contrahe localisate infectiones staphylococcal, es balanciate per un augmento in debilitate patientes de etate avantiate e in juvenissime patientes intra le hospital. Therapia a antibioticos es responsabile pro le prevention de staphylococcemia in un numero significative de casos al exterior, sed varie rationes existe pro explicar que le antibioticos ha essite minus efficace in le tractamento de patientes hospitalisate. Infectiones staphylococcal que es contrahite intra le hospital es quasi semper causate per le organismos que es "domiciliate" in le hospital. Isto significa que le racias de staphylococcos in le hospital ha supervivite al effectos del numerose antibioticos que es usate in le hospital individual. Le majoritate de iste racias es positive pro coagulase e illos produce un o plures del specific toxinas. Assi illos es etiam le racias que es le plus capace a causar serie infectiones. Iste infelice concentration de virulente micro-organismos in areas ubi le plus susceptibile individuos es albergate explica in parte le frequentia de infection staphylococcal como complication nosocomial.

Le differentias que existe inter le prognose de infectiones acquirite al hospital e le prognose de infectiones acquirite al domicilio es explicabile per characteristicas del organismo in le 2 ambientes e per le typos de patiente, specialmente con respecto al etate e al presentia de altere morbos.

Le protection de hospitalisate patientes per rigide technicas antiseptic e per le precoce e intense tractamento de omne cases de infection staphylococcal es apte a reducer grandemente le periculo del situation, sed le solution del problema del continuatemente alte mortalitate depende al minus tanto de un meliorate comprension del factores que determina le virulentia intra le organismos e le susceptibilitate intra le patiente como del disveloppamento de nove e potente antibioticos.

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CLINICAL CONFERENCE

Congenital Aortic Stenosis

By NORMAN J. SISSMAN, M.D., CATHERINE A. NEILL, M.D., FRANK C. SPENCER, M.D., AND HELEN B. TAUSSIG, M.D.

DR. NORMAN J. SISSMAN, *Moderator:* Interest in aortic stenosis has recently been greatly enhanced because of the surgical advances in its alleviation. The following 4 cases are presented to illustrate some of the problems in diagnosis and treatment of this lesion and to record 2 unusual pathologic variants.

Case 1. J.S. (HLH Number A-96356), a white girl, was observed in the Cardiac Clinic of the Harriet Lane Home from the age of 15 months until her death at the age of 5½ years.

The family history was not pertinent. There were no siblings. The patient was born at full term; birth weight was 6 pounds, 14 ounces. A heart murmur as well as unusual facies and webbed neck were noted at birth. Her psychomotor development was retarded; she was not able to sit up even with support until the age of 12 months; she began to walk only at the age of 2 years and she did not use words until the age of 3½ years. Her past medical history was negative. The only cardiac symptoms noted by the parents were slight dyspnea, fatigue, and duskiness around the lips and nose after exertion.

Physical examination at 15 months revealed an average-sized, mentally retarded child. The face was unattractive: the nose was broad and upturned, there were bilateral slight ptosis of the eyelids, a suggestion of micrognathia, and minimal bilateral webbing of the neck. There was marked bilateral cubitus valgus. The left anterior chest wall was prominent. The peripheral pulses were of good volume in all 4 extremities. The systolic blood pressure was 90 mm. Hg in the arm and 120 in the leg. The heart was moderately enlarged to the left. There was an intense systolic thrill over the entire precordium, felt best along the upper left sternal border. There was a grade-IV, long, harsh systolic murmur, loudest between the second and fourth intercostal spaces along the left sternal border, heard well over the back and in both axillae, but poorly transmitted to the great vessels of the neck. No second sound could be heard at the base of the heart on either side of the sternum. A spectrophonocardiogram taken by Dr. V. A. McKusick confirmed the auscultatory findings. It showed that the systolic murmur had the "Christmas tree" configuration usually observed in the sounds produced by the ejection of blood through a stenotic area. No clear second sound was recorded anywhere except at the localized area in the left midprecordial region; even there it was faint and had a low frequency. Fluoroscopic examination revealed the cardiothoracic ratio to be increased to about 60 per cent. The right atrial shadow was prominent. The main pulmonary artery segment was concave. The pulmonary vascularity appeared normal in the hilar areas but was slightly decreased in the periphery of the lung fields. In the left anterior oblique view, the right ventricular shadow was enlarged anteriorly and the left ventricular shadow did not clear the spinal column until the patient was rotated to an angle of 75 degrees anterior to the upright fluoroscopic table. The electrocardiogram (fig. 1) was interpreted as showing right ventricular hypertrophy and possibly also some left ventricular hypertrophy.

Examinations over the next 4 years showed little change in the cardiac findings. The blood pressure showed a narrow pulse pressure; it was 110/0 mm. Hg in the arm and 100/60 mm. Hg in the leg

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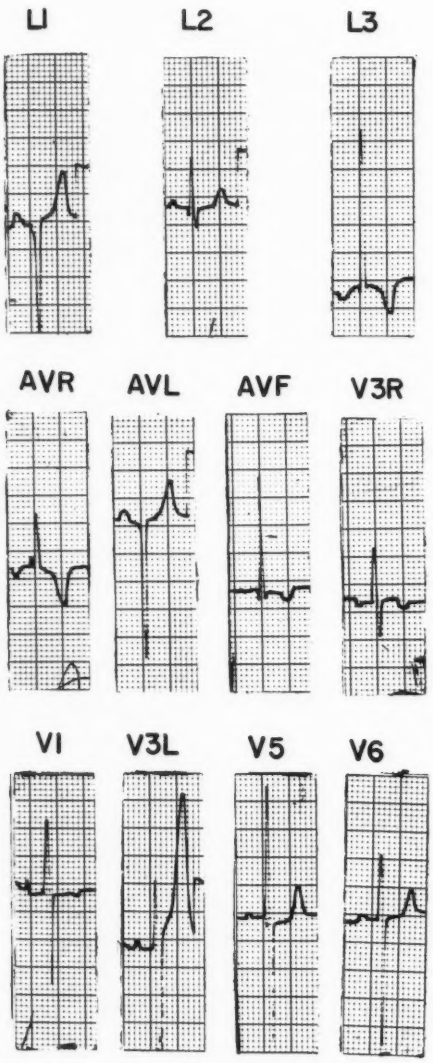

FIG. 1. Case 1. Electrocardiogram at the age of 5 ½ years. Note the deep S wave in V_1 and the tall peaked T wave in V_{3L}.

a the age of 4½, and 6 months later it was 118/68 m. Hg in the arm and 130/100 mm. Hg in the l . There was a slight increase in the cardio- oracic ratio over the 4-year period, from 59 per nt to 62 per cent (fig. 2). At the age of 3 years, t liver was palpable 7 to 8 cm. below the right stal margin; it was smooth but not tender and d not pulsate. An endocrinologic consultant re- orted a slightly advanced bone age, a female chromosomal pattern on skin biopsy, and no specific endocrinologic abnormalities. Repeated blood counts, urinalyses, and liver function tests were normal. At the age of 5 years, right heart catheterization was attempted but was unsuccessful.

The clinical diagnosis was pulmonary stenosis, either valvular, infundibular, or both. Because of the gradually but progressively increasing cardiac size, operation was recommended. This was performed by Dr. Frank C. Spencer who employed hypothermia. Systolic pressures were recorded, by direct measurement as follows: right atrium, 15 mm. Hg; left atrium, 25 mm. Hg; pulmonary artery, 30 mm. Hg; right ventricle, 175 mm. Hg. The pulmonary artery was opened and a valvular stenosis corrected. Infundibular stenosis was also noted, and this was excised from below through a right ventriculotomy. Following these procedures the right ventricular pressure varied from 25 to 75 mm. Hg and the pulmonary artery pressure was 10 mm. Hg. Although a loud systolic murmur persisted, the postoperative course appeared satisfactory until 8 hours after surgery, when she developed sudden respiratory distress and died within 10 minutes.

Autopsy (no. 27006), performed by Dr. E. Hurst, revealed combined pulmonic and aortic stenosis and pulmonary congestion. The heart was greatly enlarged. The right atrium was normal. The foramen ovale was sealed and the tricuspid valve was normal. There was extreme hypertrophy of the right ventricle; its wall measured 12 mm. in thickness. There was marked stenosis in the infundibular area; the opening in this region in the fixed state admitted only the tip of a pair of scissors. A portion of the localized constricting muscle on the medial aspect of the infundibulum had been removed surgically. The pulmonary valve revealed a ring of diminished size (10 mm. in diameter) and the cusps were thickened and distorted, especially at their free edges. Recent cuts had been made along the commissures; at autopsy the valve admitted the tip of an index finger. The pulmonary artery above the valve was slightly dilated. The pulmonary veins entered normally into the left atrium, which was normal. Examination of the mitral valve disclosed some shortening and thickening of the chordae tendineae and the valve itself seemed smaller than normal with thickening of the leaflets; however, there was no stenosis. The left ventricle was slightly hypertrophied; its wall was 16 mm. in thickness. The cusps of the aortic valve were thickened and showed slight fusion of the posterior and right commissures; the valve ring was also 10 mm. in diameter. There were thickening and scarring of the endocardium beneath the aortic valve which, together with a fibrous band that ran from the base of the aorta

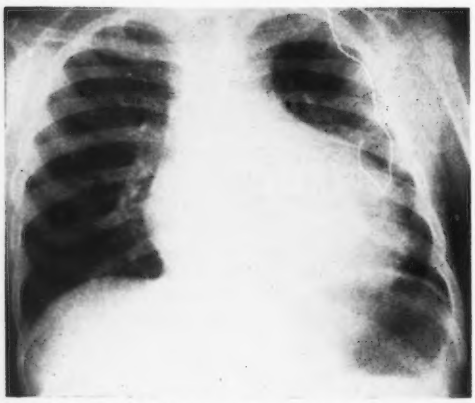

FIG. 2. Case 1. Chest x-ray, in the anteroposterior projection, at the age of 5½ years.

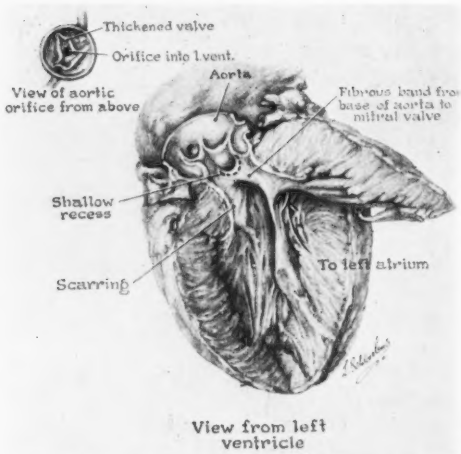

FIG. 3. Case 1. Interior of the left ventricle, showing the subaortic stenosis. Note the band of fibrous tissue extending from the base of the aorta to the mitral valve.

to the mitral valve (fig. 3), caused a subvalvular obstruction in the left ventricular outflow tract. The coronary ostia were wide and the coronary arteries had delicate walls. Blood-stained mucus was found in the bronchial tree, and the parenchyma of the lungs showed congestion and diminished aeration.

DR. SISSMAN: This is the first case of combined aortic and pulmonic stenosis with an intact septum that we have encountered in this clinic. Dr. Taussig, would you comment on some of the clinical aspects of this case that could have given us clues to the correct diagnosis?

DR. HELEN B. TAUSSIG: I think there were 3 main clinical clues. The first was the presence of left ventricular hypertrophy on fluoroscopy. Several observers thought that the left ventricle looked enlarged; others thought it was being pushed posteriorly by the enlarged right ventricle. It would have been wise to hunt for the interventricular groove in the left anterior oblique position. Usually, with extreme enlargement of the right ventricle, one can easily see the interventricular groove because it is displaced posteriorly. Secondly, the electrocardiogram differed from the pattern usually seen in cases of severe "pure" pulmonic stenosis in that lead V_1 did not show the usual tall R wave with an inverted T wave; the deep S wave in this lead should have made us suspicious of additional left ventricular hypertrophy. The tall T waves in V_3 are thought by some to be associated with left ventricular hypertrophy, although they are supposed to reflect "diastolic overload" of the left ventricle, which was not present in this case. Also, the patient did not have the high pyramidal P waves commonly seen in severe pulmonic stenosis. Thirdly, the repeated auscultatory observation that the second sound was not present on either side of the sternum or at the apex should have caused us to wonder if the aortic as well as the pulmonic valve was involved.

DR. SISSMAN: How would more detailed physiologic investigations have helped us?

DR. TAUSSIG: It is unfortunate that the right heart catheterization was unsuccessful; but had it been completed, it would have merely confirmed our clinical impression of a rather severe pulmonic stenosis. Left heart catheterization would have established the presence of obstruction to left ventricular outflow but here as with other similar cases, one must balance carefully the possible complications of such a procedure with the value of the information obtainable. I do think that, knowing this was not a typical pulmonic stenosis, we should have suggested to the surgeons that at the time of operation they

take pressures from the left-sided chambers of the heart as well as from the right; this would have enabled them to proceed differently. Had the presence of the additional aortic stenosis been recognized at the time of surgery, probably it would have been wiser to back out immediately and re-operate with use of open heart technics.

DR. SISSMAN: Dr. Spencer, Dr. Taussig has suggested a course for the surgeons! Would you tell us what you would have done had the correct diagnosis been established before the operation?

DR. FRANK C. SPENCER: There is no obvious reason why combined aortic and pulmonic stenosis, either valvular or infundibular, could not be relieved during the same operation. The best approach would include using the heart-lung machine. The actual procedure in such an instance would be to relieve the pulmonic stenosis first while on the pump without inducing cardiac standstill. After relief of this stenosis, the heart could be stopped, the aorta opened, and then the aortic stenosis relieved and the heart re-started. This method would minimize the period of cardiac ischemia.

DR. SISSMAN: In this case, in which there was a fibrous band extending from the subaortic region to the mitral valve, could the aortic subvalvular stenosis have been relieved without creating mitral regurgitation?

DR. SPENCER: Yes, by avoiding extensive resection in this area.

DR. TAUSSIG: In general, I think that the less resection there is of actual muscle, the less chance there will be of subsequent scarring. In this connection, Dr. Mary Allen Engle[1] recently described 3 cases in which there appeared to be combined valvular and infundibular stenosis of the pulmonary outflow region and in which the latter "resolved" after the relief of the valvular stenosis alone. It was postulated by her that the infundibular "stenosis" was the result of hypertrophy of the crista supraventricularis and she thinks that usually there is no necessity for surgical resection of the muscular stenosis.

DR. SISSMAN: This subaortic stenosis was fibrotic rather than muscular. Dr. Neill, would you say something about this lesion from an embryologic point of view?

DR. CATHERINE A. NEILL: There are fibrotic lesions on both sides of the heart and they extend a considerable distance down from the valves. It appears as if the chambers themselves were formed normally and the fibrosis took place at a considerably later stage in embryonic development than we are accustomed to associate with the formation of cardiac anomalies.

DR. SISSMAN: Dr. Eugene Braunwald of the National Heart Institute tells us that his group has seen 3 cases of combined aortic and pulmonic stenosis. The patients appeared with symptoms of aortic stenosis and were diagnosed by left and right heart catheterizations. A full report on these cases is being prepared. Another case of this type has already been reported in the literature.[2] This combination of lesions is certainly one for which we should be on the alert.

Case 2. S.A.C. (HLH Number B-23086), a white girl, was first seen in the Cardiac Clinic of the Harriet Lane Home in September, 1955, at the age of 19 months because of a heart murmur that had been heard at birth, failure to thrive, and episodes of "congestive failure."

The family history revealed no significant diseases. One previous pregnancy had terminated in a miscarriage at 4 months. The mother's health during this pregnancy was good. The patient was born without complication at term. The present illness dated from birth. A heart murmur had been heard at birth and persisted. She became ill on the third day of life and remained in the hospital for 2 months. During the first month she was periodically febrile and suffered from dyspnea and cyanosis, which required continuous administration of oxygen. She took her feedings poorly, and even at the age of 2 months had failed to regain her birth weight. After discharge from the hospital, she continued to do poorly. She had frequent respiratory infections, appeared pale and weak, and usually breathed heavily. Between the ages of 5 and 19 months, she had 3 episodes of what was called "congestive heart failure." These attacks were characterized by the sudden onset of irritability, prolonged continuous crying, refusal to eat, rapid respirations, pallor, and excessive sweating. Hepatomegaly and tachycardia were also noted at these times. It was because of the

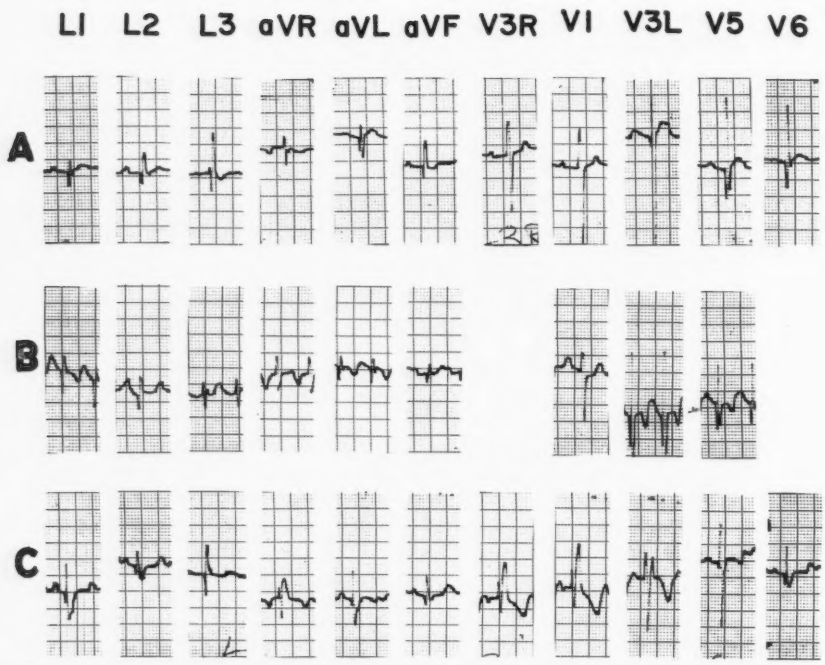

FIG. 4. Case 2. *A*. Typical preoperative resting electrocardiogram, at the age of 2½ years. *B*. Electrocardiogram during an attack of angina pectoris, age 3 years. *C*. Electrocardiogram, taken 3½ weeks after operation.

third attack of this nature that she was referred to the Cardiac Clinic.

Physical examination at the age of 19 months showed an underdeveloped, undernourished child, in acute distress with rapid respirations and suprasternal retractions. The heart rate varied from 130 to 180 per minute; the rhythm was irregular. The blood pressure was 90/60 mm. Hg in the arm and 110/70 in the leg. The left chest was prominent. The point of maximal apical impulse was 2 cm. to the left of the midclavicular line. A systolic thrill was felt along the right sternal border. There was a harsh systolic murmur which was loudest over the upper and mid-sternal areas, but could be heard over the entire precordium and back. The second sound at the base to the right of the sternum was diminished in intensity. Fluoroscopy showed the heart to be enlarged with a cardiothoracic ratio of approximately 70 per cent. In the oblique views both ventricles appeared to be enlarged. The main pulmonary artery segment was prominent and pulsated vigorously, but the peripheral pulmonary vascularity appeared normal. A barium swallow showed a left aortic arch and moderate left atrial enlargement. The electrocardiogram showed atrioventricular dissociation and frequent runs of paroxysmal ventricular tachycardia. The liver was moderately enlarged. The patient was admitted to the hospital and treated with oxygen, quinidine, and sedation. She rapidly improved. The cardiac rhythm returned to normal within 8 hours. Subsequently, an angiocardiogram was done, which showed that the right atrium and right ventricle were of normal size and shape, and the left atrium and left ventricle were moderately enlarged.

Thereafter, the patient was observed at frequent intervals in the outpatient department. She continued to have recurrent respiratory infections and spells of tachypnea; she gained weight slowly and had another spell, lasting 15 minutes, which was characterized by severe crying from apparent pain, pallor, and diaphoresis. Repeated physical examinations revealed a loud systolic murmur and thrill which were present with equal intensity along both the left and right upper sternal borders and were widely transmitted over the entire chest and great vessels of the neck. Electrocardiograms (fig. 4*A*) were interpreted as being indicative of left ventricular dominance.

In May 1957 the patient was brought to the clinic during a spell that resembled the previous

ones. Examination at that time showed her to be in acute distress with pallor, continuous crying, and marked diaphoresis. The pulse was 160 per minute and the respirations 40 per minute. The physical findings remained unchanged. An electrocardiogram taken at this time (fig. 4*B*) showed slight S-T depressions and marked inversion of the T waves in leads I, aV_L, and V_{3L} through V_6, consistent with myocardial ischemia. She was re-admitted to the hospital and responded within a few hours to treatment with morphine and oxygen. An electrocardiogram taken the following day showed reversion to its previous pattern.

Because of the character and location of the murmur and the repeated episodes of what appeared to be angina pectoris, the diagnosis of aortic stenosis was entertained. Right heart catheterization was performed, however, to determine the presence or absence of other cardiac lesions. This study showed an increase in oxygen saturation from 67 per cent to 86 per cent between the right atrium and the right ventricular outflow region. The pressure in the pulmonary artery was 36/13 mm. Hg; in the right ventricle it was 66/4 mm. Hg. The femoral artery pressure was 132/97. The pulmonary flow was approximately 4 times the systemic flow. Therefore, the diagnosis was changed to a ventricular septal defect.

In June 1957 operation was performed by Drs. H. Bahnson and F. Spencer for direct-vision closure of the lesion with the aid of a Gaertner-Kay heart-lung pump. The defect, which was small and lay in the membranous septum behind the crista supraventricularis, was closed completely. There was no evidence of aortic stenosis. Postoperatively, her course was satisfactory. When examined 3 months postoperatively, she was asymptomatic. Physical examination demonstrated only a short, soft systolic murmur along the upper left sternal border and no thrill. The heart size had decreased considerably. The electrocardiogram (fig. 4*C*) showed complete right bundle-branch block and decrease in the depth of the Q waves over the left-sided precordial leads.

DR. SISSMAN: Although this case is not one of aortic stenosis, it is included because the clinical picture was more suggestive of aortic stenosis than of a ventricular septal defect. Dr. Taussig, would you comment on the differential diagnosis of these 2 lesions?

DR. TAUSSIG: The diagnostic difficulties in this patient were the reverse of those usually encountered in childhood. More commonly, early in life the murmurs of aortic stenosis mimic those of a ventricular septal defect. Thus, in infancy and early childhood the stenotic murmur may be located quite low down along the left sternal border and does not radiate into the neck. Later, the murmur becomes loudest in the second right parasternal area and changes in character. In this case, the murmur was maximal over the base of the heart and to the right of the sternum and this, together with the absence of the usual evidence of increased pulmonary flow and the presence of attacks of angina, misled us. This is the first time I have ever seen angina in a ventricular septal defect, but I see no reason why a sudden decrease in systemic flow at times might not reduce coronary flow to such a degree as to cause temporary myocardial insufficiency, such as occurred in this patient.

DR. SISSMAN: Systemic flow at the time of catheterization was not reduced, but of course this was not determined during an anginal attack. I know of no specific studies of coronary flow in ventricular septal defects. Dr. Neill, would you comment on the electrocardiographic changes?

DR. NEILL: The S-T and T-wave changes in the electrocardiogram during the anginal attack strongly suggest myocardial ischemia. The return to the usual pattern by the following day excluded the possibility of infarction. In all the records, the Q waves in lead I and over the left side of the precordium were unusually prominent for a young child with a ventricular septal defect. The combination of these Q waves and the inverted T waves over the left precordium made us favor aortic stenosis.

DR. SISSMAN: Dr. Spencer, will you answer 2 questions for us? Were the findings at operation out of the ordinary, and, do you think the location of the defect would help explain the physical findings of aortic stenosis?

DR. SPENCER: The ventricular defect was located just proximal to the crista supraventricularis, which has been a common location for the ventricular defects in our series. The crista seemed unusually hypertrophied;

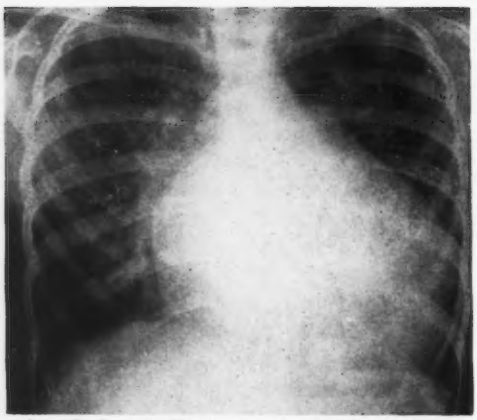

FIG. 5. Case 3. Chest x-ray in the anteroposterior projection, 1 month prior to death.

this may have given rise to the marked murmur and thrill which were present. I have no other explanation for the signs suggesting aortic stenosis.

DR. TAUSSIG: The finding of a pressure differential of 30 mm. Hg across the pulmonary valve at the time of catheterization also might be explained by the large crista.

DR. SISSMAN: Recently, there has been a report by Hancock et al.[3] from Boston concerning 7 persons over 50 years of age who were diagnosed as having aortic stenosis from their histories and physical findings, but were found subsequently to have either severe myocardial disease or unsuspected disease of the mitral valve.

DR. TAUSSIG: We have run into similar situations on several other occasions. In atypical cases, aortic stenosis remains one of our most tricky diagnostic problems.

DR. SISSMAN: This case indicates that ventricular septal defects must be included in the differential diagnosis of aortic stenosis.

Case 3. P.W., Jr. (HLH Number A-71350) was first seen in the Cardiac Clinic in July 1949 at the age of 6 years, when he was admitted to the Harriet Lane Home because of subacute bacterial endocarditis superimposed upon congenital heart disease. Thereafter, his case was followed until his death at the age of 11½ years.

The family history revealed that his maternal grandmother (see case 4 below) had congenital heart disease. Following his birth, his mother had 2 unsuccessful pregnancies, both complicated by pre-eclampsia. The mother had pre-eclampsia during this patient's gestation, and he was born prematurely. A heart murmur was heard shortly after delivery and persisted. When he was 4 months old, the mother noted minimal cyanosis during a severe upper respiratory infection. Throughout his life, his activity had been moderately restricted. He remained relatively asymptomatic until 2 months before admission, when he developed an intermittent fever, anemia, and had a severe epistaxis. He was admitted to another hospital where a diagnosis of septicemia was made and where he was treated with blood transfusions, penicillin, sulfonamide, and aureomycin. After his discharge from this hospital, his fever reappeared and petechiae were noted. Two weeks after the recurrence of these symptoms, he was admitted to the Harriet Lane Home.

On examination the heart was moderately enlarged to the left; the rhythm was regular, and the heart sounds were of good quality. There was a pathologic third sound at the apex. There was a systolic thrill along the left sternal border and a harsh systolic murmur which was audible over the entire chest but was loudest in the second and third interspace at the left sternal border. The blood pressure was 105/75 in the arm. Fluoroscopy showed a moderately enlarged globular heart. The pulmonary vessels were enlarged and pulsated more vigorously than normal. In the left anterior oblique position, the left ventricle did not clear the shadow of the spine until the patient was rotated to an angle of 85 degrees anterior to the upright fluoroscopic table. The electrocardiogram showed right axis deviation, a moderately deep Q wave and inverted T wave in lead III, and a decreased ratio of the height of the R wave to the depth of the S wave in V_1. Blood cultures established the diagnosis of subacute bacterial endocarditis due to an alpha hemolytic streptococcus. He was treated with a 6-week course of penicillin and made un uneventful recovery.

Over the next 4½ years, his heart showed striking progressive enlargement. In 1949, the cardiothoracic ratio was 53 per cent; by 1954 it had increased to 67 per cent (fig. 5). Periodic fluoroscopy indicated that the enlargement was mainly left ventricular. The electrocardiograms also showed increasing left ventricular hypertrophy: the electric axis became balanced, the voltage in the left-sided precordial leads increased, the QRS complexes showed widening and lengthening of the ventricular activation times over the left ventricle, and the ST-T segments showed changes of so-called left ventricular strain (fig. 6). Repeated physical examinations showed that the systolic murmur radiated well into the neck and ob-

secured the second sound in the second interspace to the right of the sternum. The third heart sound persisted and was interpreted as a gallop. His blood pressures averaged 100/75. The boy showed increasing dyspnea on exertion and ease of fatigability. In early 1954, he began to have attacks of dyspnea, wheezing, and coughing which resembled asthma. In late 1954, he developed frank congestive failure, which progressed despite vigorous therapeutic measures. The diagnosis of congenital aortic stenosis had been made, but, to exclude the presence of other lesions, venous catheterization was performed; this showed no shunt of blood. The pulmonary artery pressure was 70/41 mm. Hg, and the right ventricular pressure was 85/0/5 mm. Hg. The femoral artery pressure tracing showed a flat curve consistent with aortic stenosis.

Because of his intractable heart failure, an operative attempt to relieve the stenosis was recommended. A transventricular valvulotomy was performed under general anesthesia by Dr. H. Bahnson. There was great resistance to the opening of the dilator; the amount of relief obtained was questionable. After closure of the ventriculotomy, the patient developed ventricular fibrillation and died on the operating table.

Autopsy (no. 25546), performed by Dr. S. Wood, revealed that the heart weighed 650 Gm. The right side of the heart was normal. The left ventricle was greatly dilated and hypertrophied. Its wall measured 1½ cm. in thickness. The mitral valve was normal. The aortic valve measured 4 cm. in circumference at the valve ring. One centimeter above the aortic valve, the inner surface of the aorta was markedly roughened due to a heaping up of the endothelium. This roughening caused the aorta to be constricted to a circumference of 3 cm. The constricted area extended a distance of 2 cm. up the aorta from its proximal level. The changes in the aortic wall were attributed to healed subacute bacterial endocarditis. Beyond this abnormal area the aorta was normal. The aortic valve itself showed marked thickening of the valve leaflets, which must have produced a significant degree of stenosis. The coronary arteries were normal but there was diffuse scarring of the left ventricular myocardium.

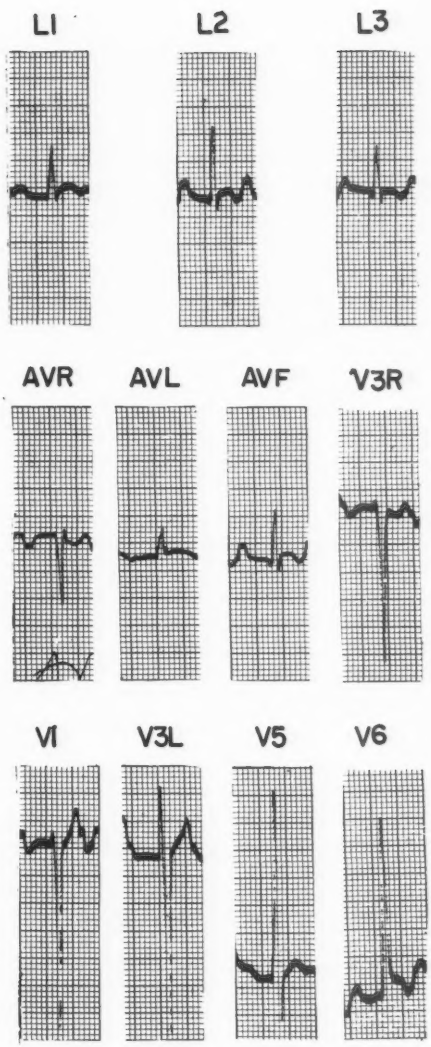

FIG. 6. Case 3. Electrocardiogram at the age of 11½ years.

DR. TAUSSIG: It should be remembered that when this patient was first seen by us in 1949, the protean manifestations of aortic stenosis were not familiar to us. It is of interest, for example, that this patient had right axis deviation in his electrocardiogram even at the age of 6 years and that the axis did not shift into the normal quadrant until after he had subacute bacterial endocarditis.

DR. SISSMAN: Was it not significant that his clinical course rapidly worsened after his endocarditis?

DR. TAUSSIG: Yes. In our present age of antibiotics, I think it is important to emphasize that many patients still do poorly despite bacteriologic cures.

DR. SISSMAN: Perhaps this is due to myocardial involvement. Perry, Edwards, et al.[4] analyzed 52 autopsied cases of subacute bacterial endocarditis and found myocardial lesions of varying degrees of severity in all but 1 case; in that one the vegetations were limited to the tricuspid valve and the mural endothelium of the right ventricle. The lesions consisted of miliary infarcts, nonspecific inflammatory changes (both interstitial and perivascular), perivascular fibrosis, actual emboli and thrombi, and petechiae. There was no direct correlation between the severity of the lesions and the presence or absence of myocardial failure but in some instances, although the changes were microscopic, they were so numerous it seemed that they must have had some deleterious effect on myocardial function. In 9 cases treated with penicillin, there was no difference in the incidence or type of lesions except that there were some additional foreign-body granulomata found. Saphir et al.[5] found a high incidence of electrocardiographic changes in patients with bacterial endocarditis who came to autopsy. These changes consisted of generalized low voltage and S-T and T-wave abnormalities which were thought to reflect myocardial disease. In our case, the electrocardiographic pattern was one of "strain" but, nevertheless, there was diffuse myocardial scarring, which probably contributed to the progressive cardiomegaly and eventual failure.

DR. TAUSSIG: Recently we have seen a 15-year-old girl who had electrocardiographic changes of left ventricular strain following a proved subacute bacterial infection. Despite pronounced physical signs of aortic stenosis, her aortic valve at operation was found to be normal.

DR. SISSMAN: Dr. Spencer, would you tell us how the surgical approach to aortic stenosis has changed since this patient was operated upon in 1955?

DR. SPENCER: The operation for congenital aortic stenosis by the introduction of a dilator through the left ventricular wall is probably quite hazardous. The stenosis is of a type that does not readily open with a dilator. Thus, with this approach, the valve may stretch and not be significantly widened; furthermore, the leaflet rather than the commissural line may tear. Also, an incision in the left ventricular wall is probably in itself hazardous. For these reasons, the open approach with extracorporeal circulation in which the stenosis is relieved under direct vision from above through an opening in the aorta is strongly preferred. In this hospital, open operation in 12 cases of congenital aortic stenosis by this method has demonstrated rather uniformly a valve with an opening of 3 to 4 mm. in diameter. The commissures have been present and there has been no calcification in any of the valves. A rather complete opening along the commissures has been made in each instance. All the patients survived operation and showed a marked decrease in the pressure gradient across the valve, although the gradient was not completely relieved. Two patients had regurgitation following the operation. Four patients in the group had subaortic stenosis; this too was resected through the aortic opening. The advantage of extracorporeal circulation is that an unhurried approach can be used to open the valve very carefully along the commissures and thus to avoid the production of later regurgitation; the advantage of the supravalvular approach is that the left ventricular wall is intact. The time actually required for the corrective procedure has varied from 10 to 15 minutes. The most encouraging reported series of open operations for congenital aortic stenosis is that of Dr. Henry Swan[6] who operated upon 11 patients, using hypothermia, and had 3 operative deaths. Of the 8 survivors 4 had some regurgitation.

DR. SISSMAN: This patient had an unusual lesion of the intima of the aorta above the valve, which has been attributed to his subacute bacterial endocarditis. Recently, we received the specimen of the heart of this patient's grandmother and it showed a congenital lesion of the aorta which was entirely supravalvular. She is the subject of our final presentation. We are greatly indebted

to Drs. J. Hirschfeld and V. H. Norwood, of Baltimore, for permission to include this case in this conference and for assistance in supplying the details of the clinical and pathologic picture.

Case 4. Mrs. A. H. (Church Home and Hospital, Baltimore, no. 93788), white, the maternal grandmother of case 3 (P.W., Jr.), died in 1956 at the age of 70 years of an acute cerebrovascular accident.

The family history was interesting. The patient was an only living child. Her mother was said to have had congenital heart disease and died during childbirth. One sister died at the age of 16 years because of heart disease which she was supposed to have had since birth. The patient had known "valvular disease" since childhood. Some degree of cardiac decompensation had been present since the age of 60 years but the symptoms had been mild and responded well to treatment with digitalis and mild diuretics such as aminophylline and ammonium chloride. Hypertension had been present since 1946, with systolic levels between 158 and 180 mm. Hg and diastolic levels between 88 and 105 mm. Hg. There was no history of rheumatic fever.

The salient cardiac findings as recorded in 1951 showed a full-sized heart which was enlarged to the left. There was a forceful thrust at the apex and an occasional extrasystole. There were "M[1] and A[1] blows"; the aortic murmur was the louder of the 2, and neither radiated to the axilla. One observer described a marked systolic murmur heard well at both the apical region and the aortic area. A chest x-ray taken in 1954 showed slight cardiac enlargement with a cardiothoracic ratio of 56 per cent. There was lengthening of the left ventricular border; the shadow of the great vessels was narrow. No electrocardiogram was taken and fluoroscopy was not done. Laboratory data showed a negative blood serology, a normal hemoglobin, and normal "routine" chemistries. She died shortly after being admitted to the Church Home and Hospital with symptoms of a cerebrovascular accident.

Autopsy (no. 1872, Church Home and Hospital), performed by Dr. V. H. Norwood, showed the heart to weigh 440 Gm. Both atria were dilated. The foramen ovale was closed and the right atrium and ventricle and the tricuspid valve were normal. The right ventricle was 4 mm. thick at a level 1 cm. below the tricuspid valve. The ventricular septum was intact. At the level of 2 cm. below the mitral valve, the left ventricular wall measured 14 mm. in thickness. The mitral valve was somewhat thickened, but otherwise it was not remarkable. The cusps of the aortic valve

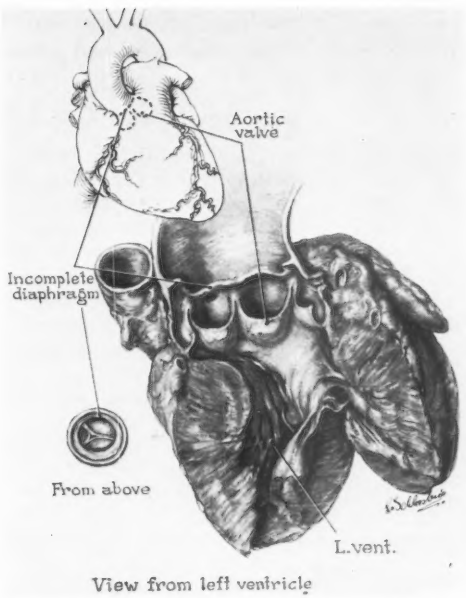

FIG. 7. Case 4. Interior of the aorta and left ventricle. Note the supravalvular constricting ring.

appeared to be shortened and thickened but movement was still possible. One to 2 cm. above the aortic valve, an annular ring, which was completely circumferential and extended into the lumen of the aorta, was found. The ring was calcified and of sufficient size to cut down the lumen of the aorta to a diameter of approximately 1 cm. (fig. 7). No sign of the ring could be seen from the exterior. The aorta distal to the ring, in the region of the origin of the innominate, the left internal carotid, and the subclavian arteries, was somewhat dilated but beyond this point it was slightly hypotrophic. The right and left coronary arteries appeared patent throughout their larger ramifications. There were mild atheromatous changes in the aorta in the thoracic and abdominal regions. Microscopically, the heart muscle fibers showed definite hypertrophy but were uniform in size. Sections from the aorta through the congenital ring showed that the ring projected as a shelf-like structure of compact hyaline collagenous tissue covered by a single layer of epithelial cells and that it made a sharp protrusion into the lumen of the vessel.

DR. TAUSSIG: This case is presented primarily because of its unusual morphology. Although the lesion undoubtedly contributed to the cardiac physical findings, it was prob-

ably not of physiologic significance, for the patient lived a normal life span and died of unrelated causes.

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Anderson, J. T., Lawler, A., and Keys, A.: Weight Gain from Simple Overeating. II. Serum Lipids and Blood Volume. J. Clin. Invest. **36**: 81 (Jan.), 1957.

Caloric intakes of 20 schizophrenic men, who were otherwise healthy, were increased without changing physical activity. Diet was constant and adequate in vitamins and protein. Carbohydrate furnished two thirds and fat one third of added calories. As a result, the proportion of calories due to fat decreased although total fat intake was higher. Calories were thus increased 8 to 39 per cent for 20 weeks. On this regimen weight gain varied from 2.5 to 22.2 Kg. (average 0.5 Kg. per week). Total serum cholesterol increased 20 mg. per cent during the first 5 weeks, but then leveled off even though gain in weight continued. On the other hand, S_f 12-20 lipoprotein increased from the tenth to twentieth week even though cholesterol was not changing at this time. There was some increase in circulating plasma and blood volume during the early part of the overeating period. The authors consider that these data support the thesis that serum cholesterol concentration is determined by the fat transport load per unit of circulation imposed on the blood.

Oppenheimer

ABSTRACTS

ATHEROSCLEROSIS

Amatuzio, D. S., and Hay, L. J.: Dietary Control of Essential Hyperlipemia. Arch. Int. Med. **102**: 173 (Aug.), 1958.

Essential hyperlipemia implies the presence of lipemic serum in fasting persons without associated diseases. Symptoms may be lacking or there may be weakness, fatigue, angina pectoris, intermittent claudication, and abdominal pain. Physical signs may include xanthomatosis, lipemic retinalis, hepatosplenomegaly, and peripheral vascular insufficiency. The fasting lipemic blood contains increased amounts of neutral fat, phospholipids, and usually cholesterol. Some investigators infer that essential hyperlipemia is not associated with arteriosclerosis. However, arteriosclerosis is often associated with essential hyperlipemia and an effort should be made to correct the elevated blood cholesterol and neutral fat. Essential hyperlipemia can usually be controlled by selectively eliminating dairy foods, coconut oil, and alcohol without other restriction in dietary fat. Certain persons may develop a fasting hyperlipemia due to these foodstuffs. The lipemic fasting serum cleared, and the esterified fatty acids, cholesterol, and phospholipids returned to normal values in 7 adults by eliminating alcohol and dairy foods and in 2 children by restricting only dairy products in the diet. The addition of either dairy foods, coconut oil, phospholipid, or ethyl alcohol to the diet caused a hyperlipemia after the serum was cleared in essential hyperlipemia.

KRAUSE

Keen, H., and Rose, G. A.: Diet and Arterial Disease in a Population Sample. Brit. M. J. **1**: 1508 (June 28), 1958.

The diet of 24 patients (10 men and 14 women) with atheromatous disease was studied. Their diet was compared to that of the same number of randomly selected controlled subjects, each pair being matched for age and sex. In the atheromatous group there was a higher intake of each of the main food materials. Statistically, the most significant differences were in the total calories and carbohydrates among the men, and to saturated fats for both sexes. The excess in the total fat intake also reached significance at the 5 per cent level. There was no evidence of a deficiency of the unsaturated or long-chain fatty acids as an etiologic agent.

KRAUSE

Cox, G. E., Taylor, B., LaVerne, G., Cox, B. S., and Counts, M. A.: Atherosclerosis in Rhesus Monkeys. Arch. Path. **66**: 32 (July), 1958.

The response of 30 adult Rhesus monkeys (18 female and 12 male) to experimental diets rich in cholesterol and total fat was studied for periods varying from several months to 3 years. Initially, the animals were kept on a stock low-fat diet of commercial ground monkey food until serum cholesterol values became relatively stabilized. Supplements of butter and cholesterol were added for the experimental diet. With the use of this diet and a one-food, one-meal-per-day technic, serum total cholesterol levels of 300 to 600 mg. per cent developed within 1 to 3 months

in the majority of animals that were adequately tested. The hypercholesteremia was interpreted as caused chiefly by the excess of dietary cholesterol, rather than the excess of dietary neutral fat. Grossly and microscopically visible atherosclerosis developed in most animals who were hypercholesteremic for prolonged periods.

MAXWELL

BLOOD COAGULATION AND THROMBOEMBOLISM

Danford, H. G., Juergens, J. L., and Barker, N. W.: Clinical Experience with Orally Administered Warfarin Sodium. Proc. Staff Meet. Mayo Clin. **33**: 359 (July 9), 1958.

Warfarin was administered to 170 patients. Certain facets of anticoagulant therapy with this drug were compared to similar data obtained in a group of 100 patients treated with a combination of Dicumarol and Tromexan. In both groups initial dosages of the drug suppressed prothrombin activity at comparable rates. During the first 72 hours, there was a slightly lower incidence of excessive hypoprothrombinemia in the warfarin group. Escape periods with a shift of the prothrombin activity above or below the therapeutic range was less common with coumadin (5 per cent) as compared to Dicumarol (9 per cent). The incidence of bleeding was small in both groups and mostly of minor degree. Vitamin K was an effective antagonist. Seventy-five per cent of the patients had normal prothrombin activity within 5 days after treatment with warfarin was discontinued. On the basis of this data, the authors claim that warfarin sodium possessed modest advantages over Dicumarol as an anticoagulant.

KRAUSE

Eiber, H. B., and Danishefsky, I.: Synthesis and Metabolism of Radioactive Heparin. Arch. Int. Med. **102**: 189 (Aug.), 1958.

Presumably, heparin acts primarily by inhibiting the formation of thrombin from prothrombin and to some extent, it prevents thrombin from converting fibrinogen to fibrin. The pharmacologic effects of heparin are confined to the blood and not the liver or other body organs. Heparin is a sulfated mucopolysaccharide normally found in animal organisms, the highest concentration being found in liver and lung, and yet its physiologic function has never been clearly defined. Heparin is found in normal blood in concentrations of 0.5 mg. per cent. By tracer technics it has been found that at least glucose and inorganic sulfate are its precursors. By the use of radioactive heparin injected intravenously in dogs, its metabolism was studied. Various dosages were used and the radioactivity of the blood and its coagulation time were then measured at intervals. The data would seem to indicate that amounts above a certain critical concentration in the blood were excreted very rapidly and thus the duration of action was not proportional to the amount administered. It appeared that the optimum dosage for an adult of 150 pounds was 50 mg. every fourth hour intravenously, and a slightly larger dose when administered intramuscularly. As a clearing factor for lipemic serum it seemed remote that a single daily or biweekly injection of heparin could have any beneficial effect.

KRAUSE

Wack, J. P., Dubuque, T., and Wyatt, J. P.: The Role of the Vertebral Venous Plexus in the Dissemination of Labeled Emboli. Arch. Path. **65**: 675 (June), 1958.

Studies were performed on dogs to determine more accurately the possible role of the vertebral venous plexus in the dissemination and ultimate sites of lodgment of embolic material. Labeled emboli made from dehydrated canine blood in which radio-iron had previously been incorporated in vivo, measurable as to size and radioactivity, offered a useful means of following these pathways. Emboli were injected into caval and vertebral venous channels with the animals in various positions to influence the volume of blood flow within the lungs. Irrespective of the route of injection, the right lung, because of its size, received a greater proportion of the emboli than the left. The prominence of the lung as the end-organ for emboli introduced into the vertebral system was a noteworthy feature of this exp rimental study, and its possible extrapolation to man was emphasized.

MAXWELL

CONGENITAL ANOMALIES

Bayer, O., and Wolter, H. H.: Hemodynamic Investigation in Tetralogy of Fallot with Reference to a New Operative Procedure. Ztschr. Kreislaufforsch. **47**: 589 (July), 1958.

In tetralogy of Fallot the pulmonary stenosis caused great resistance to flow in the pulmonary artery and shunt of venous blood to the systemic circulation. Increased resistance to flow in the aorta should reverse the direction of flow and decrease the venous admixture in the systemic circulation. This result was obtained in 10 patients with tetralogy of Fallot by graded venous infusion of arterenol; as the systemic blood pressure increased (about 30 to 40 mm. Hg), the sat-

uration for oxygen of the arterial blood improved significantly; in 1 patient the quotient systemic to pulmonary flow was measured as 2.6 before the infusion of arterenol and as 1.4 during the infusion. In view of these hemodynamic observations, a palliative operation, to produce narrowing of the proximal aorta, was proposed. The analogy with the surgically produced pulmonary stenosis in cases of interventricular septal defect was discussed. In very severe cases, a prolonged pharmacologically induced systemic hypertension may correct the hypoxia and help prepare the patient for surgery.

CALABRESI

Loogen, F., and Rippert, R.: Anomalies of the Great Systemic and Pulmonary Veins. Part I. Ztschr. Kreislaufforsch. **47**: 677 (Aug.), 1958.

Of 1,000 patients submitted to cardiac catheterization, persistent left vena cava terminating in the coronary sinus was found in 26. A diagnosis could be made because of the peculiar course of the catheter or through angiocardiography, when the left arm was used. In the 6 patients where it was the only anomaly, it did not cause any major hemodynamic disturbances. However, its recognition is important in cardiac surgery, as it must be ligated separately during open cardiac surgery, and as it may interfere with access to certain cardiac regions. In 2 additional patients a connection between the upper and lower venae cavae was present.

LEPESCHKIN

Reemtsma, K., Copenhaver, W. M., and Creech, O., Jr.: The Cardiac Conduction System in Congenital Anomalies of the Heart. Surgery **44**: 99 (July), 1958.

Disturbances of the cardiac conduction system are frequent and serious complications of intracardiac surgery. In an effort to learn more about the location of the conduction system in the human embryo and in certain cardiac defects, 8 human embryos were studied by serial coronal section through the heart and 7 human hearts with congenital defects were studied by serial sections of the area surrounding intracardiac defects. In membranous ventricular septal defects and related anomalies, the conduction bundle lies subendocardially along the posteroinferior aspect of the defect, a position that it occupies in embryonic life. Repair of the septal defect utilizing the left side of the apex of the septum is less likely to involve the conduction system because the bundle approaches the defect from the right and because the left bundle branch is a less discrete structure than the right. The etiology of heart block in intracardiac surgery is not entirely clear. In many instances the disturbance in conduction appears to be related to direct injury of the atrioventricular bundle. However, there is also evidence that factors other than direct trauma to the bundle, such as ischemia or edema, may be responsible for certain cases of heart block.

BROTHERS

Woolf, C. R., Paul, W., and Gunton, R. W.: The Diagnostic Use of an Ear Oximeter in Congenital Heart Disease. Brit. Heart J. **20**: 311 (July), 1958.

Arterial oxygen saturation decreased after exercise when a patient with a venoarterial shunt was breathing pure oxygen. This decrease was detectable by an ear oximeter. Patients with left-to-right shunts, and acquired cardiac or pulmonary disease did not show such a change although decreased arterial oxygen saturation may occur when breathing air. This test may therefore be used as a secondary test to detect venoarterial shunts and as an aid in difficult cases for the detection of bidirectional shunts, the cause of cyanosis in patients with combined pulmonary and congenital heart disease, the differentiation of acquired from congenital heart disease, and for the selection of patients for surgical treatment.

SOLOFF

CONGESTIVE HEART FAILURE

Fejfar, Z.: Haemodynamic Changes in Cardiac Failure. Acta cardiol. **13**: 228, 1958.

The data available in the literature on changes in blood flow to various organs in acute and chronic cardiac failure were reviewed. While cerebral and hepatic blood flows declined in proportion to the decrease in cardiac output, the diminution in renal blood flow was greater. The increase in venous pressure of patients in congestive failure was due not only to increased blood volume or to the shifting of blood from arterial to the venous vessel, but also to venoconstriction: the evidence for this was that sympatholytic drugs induced a greater fall in venous pressure in patients in failure than in normal persons. There was no evidence that the coronary blood flow declined in cardiac failure. These hemodynamic changes were not specific for cardiac insufficiency; they were present also in other types of circulatory insufficiency. The hypothesis was advanced that a low myocardial oxygen tension caused coronary vasodilatation and secondary peripheral adjustments, through nervous and humoral mechanisms; and that these changes produced the hemodynamic phenomena characteristic of failure of the circulation. The

afferent and efferent pathways and the central integration of these hypothetical reflexes are, however, unknown.

CALABRESI

CORONARY ARTERY DISEASE

Himbert, J., Boumard, B., and Lenègre, J.: Prognosis and Treatment of Collapse following Myocardial Infarction (Study of 66 Observations). Arch. mal. coeur **51**: 728 (Aug.), 1958.

Of 472 consecutive patients with recent myocardial infarction, 66 showed collapse, defined as a systolic pressure of 80 mm. or less. The total mortality among these patients was 72.7 per cent. It was 84 per cent in patients with and 68 per cent in those without previous arterial hypertension; 66 per cent in first and 89 per cent in second or third infarction; 78 per cent in primary and 64 per cent in secondary collapse; 93 per cent the first day, 76 per cent the first week, 75 per cent the second and 50 per cent the third week; 95 per cent if the systolic pressure was initially less than 50 mm. and 62 per cent if it was more; 84 per cent in the presence of major signs of shock, 65 per cent in the presence of minor signs, and 40 per cent in their absence; 89 per cent in the presence and 60 per cent in the absence of major heart failure. The mortality was 74 per cent in patients treated with norepinephrine, 75 per cent in those treated with phenylephrine and 76.5 per cent in those treated with minor vasopressor drugs; in all treated patients it was 66 per cent when treatment was immediate and 100 per cent when it was delayed. When this factor, as well as the peculiarity of each case, was considered, norepinephrine seemed to have had the greatest effect. It caused a pressor effect in 59 per cent and disappearance of shock in 33 per cent of the patients. The possible causes of the therapeutic failures and methods of their prevention are discussed in detail.

LEPESCHKIN

Faivre, G., Gilgenkrantz, and Tenette: Perforated Septal Infarction. Thrombosis of the Perforation Originating Multiple Pulmonary Emboli. Arch. mal. coeur **51**: 683 (July), 1958.

The clinical and pathologic findings in 1 case of myocardial infarction with perforation of the interventricular septum were reported. At autopsy it was found that the perforation was partially occluded by thrombotic deposits. There was extensive pulmonary infarction, probably secondary to emboli originated from the septal thrombus. The pertinent literature is reviewed, with reference to this complication and to the hemodynamic effects of acquired septal defect.

CALABRESI

Biörck, G., Blomqvist, G., and Sievers, J.: Studies on Myocardial Infarction in Malmö 1935-1954. II. Infarction Rate by Occupational Group. Acta med. scandinav. **161**: 21, 1958.

This report deals with the frequency of myocardial infarction in certain occupational groups as determined by a study of patients so afflicted in the hospitals of Malmö during the period 1935 to 1954. A number of published reports dealing with this aspect of the epidemiology of coronary artery disease are reviewed. Occupationally active patients were subdivided into 3 groups: employers, clerks and workers; and age specific infarction rates were calculated for the men. In the employer group, consisting mainly of men with small enterprises, there was a significantly higher infarction rate than in clerks and workers. There were no significant rate differences between clerks and workers. For women, the differences between the various occupational groups were not significant. There was a higher infarct rate among married people than among single, widows, widowers, and divorced people. These data on occupational groups point in the same direction as some recent British statistics. The authors believe that the causal factors behind these observations ought to be studied more intensively in order to disclose whether any preventive measures may be undertaken.

BROTHERS

Freeman, W. J.: The Histologic Patterns of Ruptured Myocardial Infarcts. Arch. Path. **65**: 646 (June), 1958.

In 36 patients (20 men and 16 women between the ages of 37 and 89) in whom death was caused by rupture of the myocardium after infarction due to arteriosclerosis, the commonest intervals between clinically apparent infarction and death were less than 24 hours and from 3 to 7 days. Histologic examination of the hearts demonstrated multiple superimposed infarcts, the usual pattern being that of multiple subendocardial infarcts of an indicated age of 3 to 7 days, surrounded by a very recent transmural infarct, associated with a single occlusive thrombus in a major coronary artery. Indirect evidence indicated that the older, smaller infarcts were caused by partial obstruction of the major vessel at the site of eventual thrombosis. Rupture appears most likely to occur when (1) ischemia due to partial obstruction of a major artery has caused focal necrosis in the inner portion of the ventricular wall; (2) thrombosis of the artery at the site of partial obstruction has followed the ischemic necrosis by 3 to 7 days, when necrosis was advanced and a maximal polymorphonuclear infiltrate was present; (3) ischemic contracture of the ventricular wall

has abated. It may also occur through a transmural infarct more than a few days old, in which the process of repair has not proceeded rapidly enough to support the deteriorating necrotic muscle.

MAXWELL

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Tallon Cantero, R.: Contribution to the Pathogenesis of the Wolff-Parkinson-White Syndrome. Arch. mal coeur **51**: 779 (Aug.), 1958.

A patient with a typical Wolff-Parkinson-White pattern in the electrocardiogram at rest showed later appearance, shorter duration, and lower voltage of the delta wave after exercise and atropine, while the P-S interval remained unchanged. Sympatol caused slightly earlier appearance and increased duration and voltage of this wave while the P-S interval remained unchanged. The delta wave is attributed in this case to delayed excitation of part of the atrium.

LEPESCHKIN

Rijlant, P.: Global Electrogenesis in Man. Vectorial Electrocardiography and Vectorcardiography. Acta cardiol. **13**: 349, 1958.

A system of multiple combined leads was described. Vectorial loops in 3 perpendicular planes were recorded synchronously: a cinematographic camera was used to record sequential images of the developing loops. The planar vectorial deflections were also recorded on a kymograph; this technic gave a record similar to that of conventional electrocardiography, and also permitted a better analysis of the S-T segment and of the T waves. Experiments on a chest model were described to prove that proximity effects were corrected by the method adopted. It was found that in normal young adults the electrical activity of the ventricles had no significant component outside of a single plane. This plane was usually oblique from the right shoulder to the left hip and from the back anteriorly. In a group of other healthy young adults with a history of severe diseases in the past, the sequential ventricular instantaneous vectors were located in more than 1 plane or in a twisted surface. In older, normal adults, the distribution of the sequential vectors remained in 1 plane, although its orientation became horizontal or even ascending. This analysis was essentially limited to the opening deflection of the normal electrocardiogram (QRS); discordant changes of the T plane have, however, been noted. In cardiac patients the electrical activity was usually distributed in 2 or 3 planes or in a twisted surface; it remained in 1 plane however in left bundle-branch block. Extrasystoles remained also localized to 1 plane. The uniplanar distribution prevailed also in the dog and in the rabbit; investigation in these animals is still in progress; experimental interferences induced more important deviation from the uniplanar distribution for the phase of recession (T deflection) than for the vectors of accession.

CALABRESI

Schlicht, L.: The Kymogram of Degenerative Changes in the Wall of the Iliac Artery during Lumbar Aortograph. Fortschr. Geb. Röntgenstrahlen **88**: 680 (June), 1958.

Stenosis of the lumen was characterized by a flailing movement of the artery proximal to the narrowing. Weakening of the arterial wall in a lateral direction resulted in increased pulsatile movement and a caterpillar-like contour; weakening of a longitudinal direction resulted in bowing and elongation of the vessel, with increased pulsation at the apex of the arch. Complete loss of elasticity resulted in loss of pulsation. The increased pulsatile movement in itself led to further degenerative changes, resulting in a vicious circle.

LEPESCHKIN

Meyer-Heine, A., Chartrain, E., Kervoelen, P., and Quillec, A.: Diagnosis of Stenosis at the Aortic Orifice by means of Registration of the Carotid Pulse. Arch. mal. coeur **51**: 705 (Aug.), 1958.

In 40 patients with valvular aortic stenosis the right carotid pulse, registered with a carefully placed condensor microphone on a cathode ray oscilloscope, showed 4 types. Type I showed normal form with vibrations superimposed on the systolic plateau; it corresponded to mild stenosis. Type II showed a short vibratory plateau followed by an ascent; it corresponded to medium stenosis. Type III showed a prolonged ascent (more than 0.1 second) with a vibratory terminal portion; it corresponded to pronounced stenosis. The systolic vibrations were seen in only 1 of 1,500 patients without aortic stenosis (this patient had persistent ductus). Type IV showed a prolonged ascent of uniform slope and pointed summit, which may show vibrations or notches; it corresponded to very severe stenosis, and was observed especially in calcific stenosis. The last 3 types may show absence of the dicrotic wave. The relation between the degree of stenosis and the type of curve was confirmed through study of the effects of valvulotomy and experimental

stenosis in animals. The typical configuration may be modified slightly by the presence of aortic sclerosis and left ventricular failure.

LEPESCHKIN

Abel, H., Briske, I., Engelking, A., Gartner, W., and Schaefer, H.: The Effect of Gradients of Temperature of the Ventricular Wall on the Ventricular Electrocardiographic Gradient. Acta cardiol. **13**: 278, 1958.

The hypothesis that a difference of temperature in the ventricular wall is an important factor in the ventricular gradient, and therefore of the concordant T wave was studied. The electric ventricular gradient was measured only in its frontal projection; to influence the gradient of temperature from the epicardium to the anterior chest wall in man, a heating pillow of adequate shape and temperature was used; in the dog the intraparietal differences in temperature were measured by a needle implanted in the ventricular wall and provided with multiple well-isolated copper-constantan joints; the temperature of the epicardial surface or of the blood reaching the left ventricular wall was artificially changed. In man, if the anterior chest wall temperature was increased, the amplitude of the electric ventricular gradient increased in most of the cases. In the dog, when the variations of temperature across the ventricular wall were similar at the apex and at the base, no relation was found between the amplitude of the ventricular gradient and the temperature gradient. The difference of temperature between the blood in the right and in the left cardiac chambers had little influence on the T wave; more important was the gradient of temperature of the left ventricular wall. It was also noted that there was no relation between the size of the heart, in different species or among children and adult men, and the ventricular gradient. It was concluded that, although differences in temperature are a factor contributing to the electric ventricular gradient, its amplitude largely depends on other still unknown factors.

CALABRESI

Pieri, J., Jouvé, A., Casalonga, J., Nicolai, P., and Ambrosi, C.: Comparative Study of Surface and Intrathoracic Leads in Man. Acta cardiol. **13**: 327, 1958.

In 4 normal subjects and in 6 cardiac patients the electrocardiographic records obtained from esophageal or bronchial unipolar electrodes were compared with the unipolar electrocardiograms from multiple thoracic leads. These leads were arranged in 4 parallel horizontal planes passing through the second, third, fourth, and fifth intercostal spaces, and along vertical lines drawn through the points of V_1, V_2, V_4, V_6, $_4R$, $_8R$, and symmetrical posterior points. It was found that in most cases the contour of the intrathoracic leads corresponded to the contour expected from the chest leads, and that the proximity of the intrathoracic leads to the heart had little influence; exceptions to the regularity of the sequential leads were found primarily in patients with right bundle-branch block.

CALABRESI

Luisada, A. A., Liu, C. K., Aravanis, C., and Testelli, M.: Intracardiac Vibrations of Sonic Frequency within the Right and Left Hearts. Acta cardiol. **13**: 338, 1958.

A method was presented for recording sonic frequency vibrations transmitted through the column of fluid of a common cardiac catheter, using amplifier circuits and filters previously described. Experiments in vitro and in animals were reported, indicating that the records obtained result from sonic vibrations of the blood within the cardiac chamber in which the tip of the catheter was placed. The characteristics of the tracings obtained in the various cardiac chambers and in the aorta and pulmonary artery were described. More extensive study, including cases of valvular lesions, are being reported.

CALABRESI

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Song, Y. S., and Sprunt, D. H.: Nonbacterial Diffuse Myocarditis Associated with Interstitial Pneumonia. Arch. Path. **65**: 666 (June), 1958.

Three patients with nonbacterial pancarditis occurring under 2 years of age were presented. They were morphologically identical with those of isolated or diffuse interstitial myocarditis of unknown etiology. A moderate degree of interstitial pneumonia was noted in each case, which on morphologic evidence was probably due to a virus infection. No pathogenic organisms were demonstrated by the repeated cultures of blood, lungs, spinal fluid, and spleen and by microscopic studies of the sections of the heart and lungs. The data from these patients would suggest that a virus infection may be linked with myocarditis which involved the entire heart.

MAXWELL

Fremont, R. E., Losner, S., and Volk, B. W.: The Fibrinogen Polymerization Test in Nonspecific Myocarditis and Pericarditis. Arch. Int. Med. **102**: 41 (July), 1958.

The fibrinogen polymerization test is based upon the persistence of fibrinogen in citrated serum following gross coagulation of whole blood

to which a critical dose of heparin has been added. The phenomenon is believed to be due to interference with the polymerization of fibrinogen by heparin. This test was compared with other acute phase reactants such as the C-reactive protein, the erythrocyte sedimentation rate, plasma fibrinogen concentration, and also the antistreptolysin-O titer. These tests were carried out serially in 22 patients with nonspecific myocarditis and pericarditis, active rheumatic fever with myocarditis, and a miscellaneous group (including patients with tuberculous pericarditis, acute pericarditis, associated with inactive heart disease, atypical coronary artery disease and beriberi disease). The fibrogen polymerization test was consistently positive in all patients with nonspecific myocarditis and pericarditis as well as in those with myocarditis and pericarditis associated with rheumatic valvular disease. On the other hand, it was negative in the other conditions studied. Of the acute phase reactants, only the erythrocyte sedimentation rate was usually abnormal. These results suggested that the fibrinogen polymerization test may serve as a valuable aid in the differential diagnosis of acute nonspecific myocarditis and pericarditis. It may also be useful to exclude other conditions resembling nonspecific myocarditis such as beriberi heart disease or atypical coronary artery disease. Perhaps the most important feature of the fibrinogen polymerization test, in contrast to all nonspecific nonreactants, was the fact that it was not readily suppressed by salicylate or steroid therapy. This would suggest its further usefulness as a criterion for the efficacy of therapy.

KRAUSE

HYPERTENSION

Locket, S.: A New Orally Effective Long-Acting Ganglion-Blocking Agent for Hypertension (189c56). Brit. M. J. **2**: 74 (July 12), 1958.

The author details case reports on 11 severely hypertensive patients treated with pentacynium methylsulfate, 189c56, a derivative of the group of ganglionic-blocking substances. Valuable features are enthusiastically described for the drug. Because it was invariably effective when used orally and when given daily before breakfast, the expected degree of fall in blood pressure was obtained. Its duration of action permitted control of hypertension in some patients with a single daily dose. Dosage of the drug was highly critical and a small alteration in the controlling dose of 5 to 12 per cent may cause a marked effect on the extent and duration of the hypotension. Side effects were minimal because constipation rarely occurred and, even with large doses, disturbances in bladder emptying were not evident.

KRAUSE

Cox, J. R., and Daly, J. J.: Effects of Pentacynium Methylsulphate on Renal Circulation in Hypertension. Brit. M. J. **2**: 78 (July 12), 1958.

Some ganglionic-blocking drugs cause a fall in renal blood flow. Reportedly, the administration of pentacynium, which is a ganglionic-blocking agent, was not associated with changes in effective renal blood flow (ERBF) or glomerular filtration rate (GFR) though a prolonged fall in blood pressure was obtained. Hence, the authors studied the effects of the drug on the renal circulation of 9 patients with hypertension. In all subjects there occurred a fall in blood pressure to normal levels and this fall persisted for at least 16 hours. Initially, after a period of 30 minutes, a reduction in ERBF and GFR occurred in all patients; by 60 to 110 minutes the mean ERBF and GFR had risen in 4 patients to 50 per cent of the mean control value. In 2 patients with severe renal damage, the ERBF and GFR had risen to greater than their control values by the end of 110 minutes. These observations lend support to the view that the changes in ERBF may be independent to some extent of changes in blood pressure. The unexpected rise in ERBF and GFR in these 2 patients may have been due to renal vasodilatation.

KRAUSE

Hall, C. E., and Hall, O.: Relative Resistance to the Hypertensive Effects of Desoxycorticosterone During Active Phase of Renal Compensatory Hypertrophy. Am. J. Physiol. **194**: 236 (Aug.), 1958.

An attempt was made to ascertain the circumstances under which unilateral nephrectomy maximally sensitized rats to hypertensive cardiovascular disease induced by desoxycorticosterone acetate in the presence of augmented salt intake. The experiments showed that animals in which hormone treatment was delayed until 2 weeks after uni-nephrectomy were much more sensitive than animals in which hormone treatment was begun on the day of kidney removal. This was indicated by earlier onset and greater severity of hypertension; by a larger percentage of animals in such groups being affected, and by a greater incidence and severity of cardiovascular lesions in the former as compared with the latter. The much greater kidney size of the former clearly makes it difficult to ascribe the greater sensitivity to a reduction in renal mass as such. It is thought that during active compensatory renal hypertrophy the renal tubules are probably less responsive to the action of the hormone and therefore less prone to develop sodium retention and hence hypertension.

WENDKOS

AMERICAN HEART ASSOCIATION, INC.

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Telephone Gramercy 7-9170

ARTERIOSCLEROSIS SOCIETY JOINS AHA AS A COUNCIL

The American Heart Association is proud to announce that the American Society for the Study of Arteriosclerosis has joined the American Heart Association. The Society has become the Council on Arteriosclerosis. The Society's action, which followed a vote in favor of the amalgamation by a large majority of the membership, brings to eight the number of Councils now functioning within the Heart Association framework.

In a letter welcoming the Society as a new AHA Council, Francis L. Chamberlain, M.D., President of the American Heart Association said:

"The standards and achievements of the American Society for the Study of Arteriosclerosis have always been of the highest order, and I am convinced that pooling of the experience and energies of our two organizations will accelerate advances toward the ultimate conquest of arteriosclerosis."

The new AHA Council will hold a scientific session and a symposium as part of the Heart Association's 32nd annual Scientific Sessions in Philadelphia, October 23-25, following an independent Council meeting in the Spring. Elected as officers of the Council on Arteriosclerosis are: J. C. Paterson, M.D., London, Ontario, Canada, Chairman; Forrest E. Kendall, Ph.D., New York, Vice-Chairman; O. J. Pollack, M.D., Dover, Del., Secretary; and Aaron Kellner, M.D., New York, Program Chairman.

ABSTRACTS OF PAPERS AND EXHIBIT APPLICATIONS DUE JUNE 12 FOR AHA SESSIONS

Official forms for the submission of abstracts may now be obtained by those wishing to present *papers* at the annual Scientific Sessions of the American Heart Association, to be held October 23-25 in Philadelphia. These forms may be requested by writing to F. J. Lewy, M.D., Assistant Medical Director of the American Heart Association, and must be returned postmarked no later than June 12.

Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must

MORE HEART ASSOCIATIONS AID NATIONAL RESEARCH PROGRAM

A total of $105,895 has been provided by affiliates and chapters through January 15, 1959 to help underwrite the total of $3,062,204 awarded for the 1958-59 fiscal year under the national research support program of the American Heart Association. This sum is in addition to funds regularly assigned to the national research program by Heart Associations throughout the country.

Heart Associations which have provided funds to be applied to AHA-supported grants and fellowships, in addition to those listed in the September and November issues of *Circulation,* are:

Hartford (Conn.) Heart Association, which previously contributed $1400, provided the balance of $5200 for a $6600 grant in full support of Averill A. Liebow, M.D., Yale University School of Medicine; New Jersey Heart Association, $7000 in partial support of the grant of Milton Helpern, M.D., Office of Chief Medical Examiner, City of New York.

be limited to 250 words or less and should contain a brief digest of the results obtained and the conclusions reached. Applications will be screened by the Association's Committee on Scientific Sessions Program.

Applications for space for *scientific exhibits* should be filed with the Association through Dr. Lewy, postmarked no later than June 12, 1959. Applications for *industrial exhibits* may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, N.Y.

PROCEEDINGS OF ASSOCIATION'S 31ST SCIENTIFIC SESSIONS ARE STILL AVAILABLE

Copies of the *Proceedings of the 31st Scientific Sessions* of the American Heart Association held in San Francisco, October 24-26, 1958, containing 342 abstracts of current investigative work, including 90 papers presented during the meeting, are still available to physicians and scientists.

Of special interest in the proceedings are summaries of the Lewis A. Conner and George E. Brown Memorial Lectures. The abstracts are arranged in alphabetical order according to senior author, making them a useful reference to all physicians interested in cardiovascular disease. The 143-page, paper-bound volume is obtainable at $2.00 a copy from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

1958 ANNUAL REPORT OF AHA EMPHASIZES RESEARCH GAINS

The recently issued 1958 Annual Report of the American Heart Association, entitled "Saving Lives," emphasizes the gains in therapy and prevention in the field of heart and circulatory diseases achieved through research since the Association's reorganization as a national voluntary health agency in 1948.

Included in the report are consolidated financial statements of the Association and all its affiliates, as well as a breakdown of financial expenditures covering the past five fiscal years of the national office of the AHA.

HEART BULLETIN DISTRIBUTED BY MANY HEART ASSOCIATIONS AS SERVICE TO PHYSICIANS

As part of their program of services to physicians, local Heart Associations and health departments purchase nearly 50,000 copies of each issue of *The Heart Bulletin* for distribution to practicing physicians. *The Heart Bulletin* is now sponsored by the American Heart Association in cooperation with the National Heart Institute and the American Academy of General Practice.

Among the interesting and useful presentations for the practicing physician and internist in the March–April issue of *The Heart Bulletin* are the following:

"Arteriosclerosis Obliterans," John L. Juergens, M.D. and John F. Fairbairn, II, M.D.; "Raynaud's Disease," Ray W. Gifford, Jr., M.D.; "Cor Pulmonale, Part 2, Therapeutic Considerations," Peter C. Luchsinger, M.D. and Kenneth M. Moser, M.D.; "Spatial Vectorcardiography," Arthur Grishman, M.D.; and "Treatment of Infants With Heart Failure," Saul J. Robinson, M.D.

The Heart Bulletin was initiated in 1952 as a public service by the Medical Arts Publishing Foundation, Houston, which continues to publish the journal bimonthly.

PULMONARY CIRCULATION VOLUME IS PUBLISHED

Transactions of the International Symposium on Pulmonary Circulation, held in Chicago on March 20, 1958 under the sponsorship of the Chicago Heart Association, have been published by Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, N. Y. The price of the volume is $4.50.

Edited by Wright Adams, M.D. and Dr. Ilza Veith, the book provides an extensive review of the subject of pulmonary circulation. Included are results of recent research, clinical applications of such research and stimulating discussions among leading specialists in the field. The 368-page volume contains 127 illustrations.

MEETINGS CALENDAR

April 6-9: American Academy of General Practice, San Francisco. Mac F. Cahal, Volker B'lvd. at Brookside, Kansas City 12, Mo.

April 12-13: American Society for Artificial Internal Organs, Atlantic City. Charles K. Kirby, 110 Maloney Building, Philadelphia, Pa.

April 15-17: American Surgical Association, San Francisco. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 20-24: American College of Physicians, Chicago. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

May 3: American Federation for Clinical Research, Atlantic City. George E. Schreiner, Georgetown University Hospital, Washington 7, D.C.

May 3-4: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Avenue, New York 16, N.Y.

May 5-6: Association of American Physicians, Atlantic City. Paul B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 26-29: American College of Cardiology, Philadelphia. Philip Reichert, 480 Park Avenue, New York 22, N.Y.

June 3-7: American College of Chest Physicians, Atlantic City. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

June 8-12: American Medical Association, Atlantic City. F. J. L. Blasingame, 535 N. Dearborn Street, Chicago 10, Ill.

August 10-13: National Medical Association, Detroit. John T. Givens, 1108 Church Street, Norfolk, Va.

September 28-October 2: American College of Surgeons, Atlantic City. Michael L. Mason, 40 E. Erie Street, Chicago 11, Ill.

October 19-23: American Public Health Association, Atlantic City. B. F. Mattison, 1790 Broadway, New York 19, N.Y.

October 23-27: American Heart Association Annual Meeting and Scientific Sessions, Philadelphia. American Heart Association, 44 East 23rd Street, New York 10, N.Y.

ABROAD

July 27-30: Shaio Foundation Symposium on Cardiovascular Diseases, Bogota, Colombia. Alberto Vejarano-Laverde, 43-23 Carrera 13, Bogota-Colombia.

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